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(54) Title: A METHOD OF TREATING CANCER

(57) Abstract

The present invention relates to a method of treating cancer which comprises administering to a mammalian patient a compound which inhibits MEK and a compound which inhibits farnesyl protein transferase.

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TITLE OF THE INVENTION
A METHOD OF TREATING CANCER

BACKGROUND OF THE INVENTION

The present invention relates to a method of treating cancer using a compound which has MEK inhibiting activity and a compound which has farnesyl protein transferase inhibiting activity.

The Ras protein is part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation, Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem. 62*:851-891 (1993)). Activation of Ras leads to activation of multiple intracellular signal transduction pathways, including the MAP Kinase pathway and the Rho/Rac pathway (Joneson *et al.*, Science *271*:810-812).

Mutated *ras* genes are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa^1-Aaa^2-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al., Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein

transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem. 61*:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics 30*:209-237 (1992)).

The Ras protein is one of several proteins that are known to undergo post-translational modification. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell, 62*:81-88 (1990); Schaber *et al.*, *J. Biol. Chem., 265*:14701-14704 (1990); Schafer *et al.*, *Science, 249*:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA, 87*:7541-7545 (1990)). Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, *et al.*, *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, *et al.*, have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first class includes analogs of farnesyl diphosphate (FPP), while the second is related to protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation.

(Schaber *et al., ibid*; Reiss *et. al., ibid*; Reiss *et al., PNAS, 88*:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al., Science, 260*:1934-1937 (1993); Graham, et al., *J. Med. Chem., 37*, 725 (1994)).

Inhibition of farnesyl-protein transferase has been shown to block the growth of *ras*-transformed cells and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al., Science, 260*:1934-1937 (1993) and G.L. James *et al., Science, 260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al., Proc. Natl. Acad. Sci U.S.A., 91*:9141-9145 (1994)) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al., Nature Medicine*, 1:792-797 (1995)).

Other studies suggest that isoprenylation of certain isoforms of Ras is resistant to treatment with farnesyl-protein transferase inhibitors. For example, Ki-Ras can be farnesylated or geranylgeranylated *in vitro* (James et al, *J. Biol. Chem.* 270, 6221-6226 (1995)). This effect may contribute to the resistance of certain cell lines containing activated Ki-*ras*- to treatment with farnesyl-protein transferase inhibitors (E.C. Lerner et al., *J. Biol. Chem.* 270, 26770-26773 (1995); G. James et al, *Proc. Natl. Acad. Sci.* 93, 4454-4458 (1996)).

Resistance to the growth inhibitory properties of farnesyl protein transferase inhibitors has been associated with the absence of down-regulation of the MAP kinase pathway (L. Sepp-Lorenzino et al, *Cancer Res.* 55, 5302-5309 (1995)). Certain isozymes of the Map/ERK kinases (MEK's) are components of the canonical MAP kinase cascade, which also contains Raf and ERK (M.H. Cobb et al., *J. Biol. Chem.* 270 14843-12846 (1995)). This cascade is initiated by activated Ras, which binds directly to Raf, resulting in Raf's activation. The activated Raf

then phosphorylates and activates MEK, which in turn phosphorylates and activates ERK.

MEK inhibiting compounds in general inhibit the phosphorylation of threonine and tyrosine residues on ERK which occurs naturally in the Map kinase pathway as a result of many diverse extracellular stimuli. Many oncogenes and growth factors, including *ras* , *raf*, epidermal growth factor and platelet-derived growth factor, activate the MEK signal transduction pathway. Examples of cancers where the MEK pathway is implicated therefore include cancers where these oncogenes and growth factors are proposed to play a role, including cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung. More particularly, such examples include histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers. More particularly, such cancers include pancreatic and breast carcinoma.

A MEK inhibiting compound and a farnesyl protein transferase (FPTase) inhibitor are used in the present invention to inhibit the growth of cancer cells that are resistant to inhibition by FPTase inhibitors alone.

SUMMARY OF THE INVENTION

A method of treating cancer is disclosed which is comprised of administering to a mammalian patient in need of such treatment an amount of a MEK inhibiting compound and an amount of a farnesyl protein transferase inhibiting compound which are effective to treat cancer.

DETAILED DESCRIPTION OF THE INVENTION

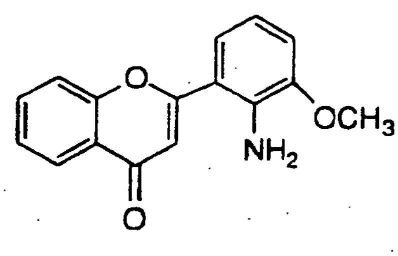
The present invention relates to a method of treating cancer which is comprised of admininstering to a mammalian patient in need of such treatment an effective amount of a MEK inhibiting compound and an effective amount of a farnesyl protein transferase inhibiting compound. Any compound which inhibits MEK and any compound which inhibits farnesyl protein transferase can be used.

As used herein the term "MEK inhibiting" is used in the general sense to relate to compounds which antagonize, inhibit or counteract the activity of the MEK cascade or the proteins produced in response thereto. In particular, the term is used to refer to compounds which inhibit or antagonize the activity of the enzyme Map/Erk kinase, or the gene coding Map/Erk kinase.

The term farnesyl protein transferase inhibiting compound is likewise used in the general sense and refers to compounds which antagonize, inhibit or counteract the activity of the gene coding farnesyl protein transferase or the protein produced in response thereto.

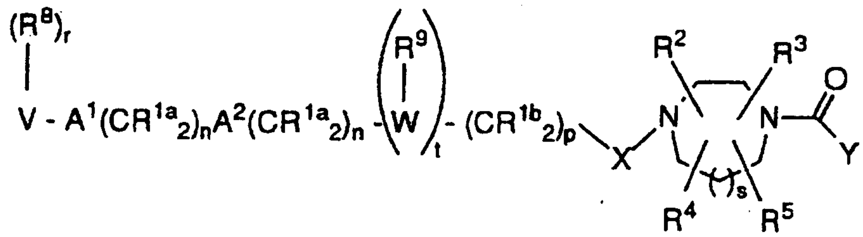
Cancers which are treatable in accordance with the invention described herein include cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx, liver and lung. More particularly, such cancers include histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers. Additional examples include cancers in which overexpression or activation of Raf-activating oncogenes (e.g., K-*ras*, *erb*-B) is observed. More particularly, such cancers include pancreatic, mammary and salivary carcinomas, colorectal carcinoma, exocrine pancreatic carcinoma and myeloid leukemias.

Examples of compounds which inhibit MEK are as follows:

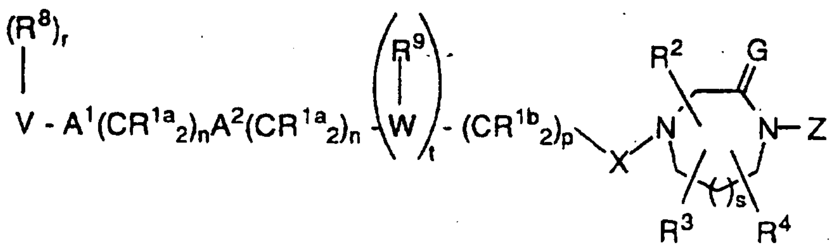


Examples of farnesyl protein transferase inhibiting compounds include the following:

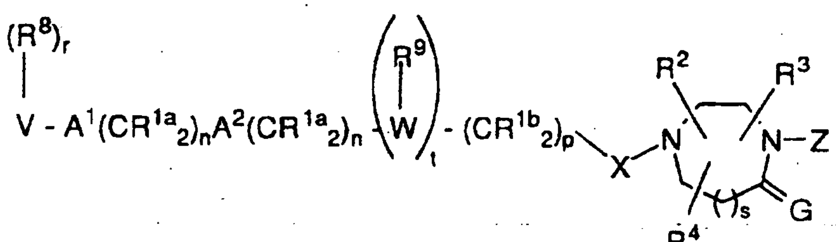
(a) a compound represented by formula (II-a) through (II-c):



(II-a)

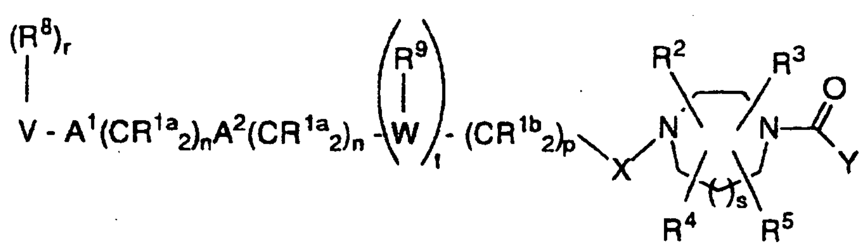


(II-b)



(II-c)

wherein with respect to formula (II-a):



(II-a)

or a pharmaceutically acceptable salt thereof,

R^{1a} and R^{1b} are independently selected from:

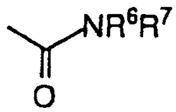
a) hydrogen,

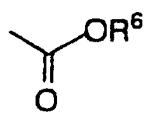
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl,

C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,



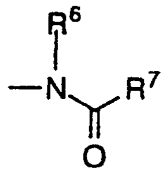
or


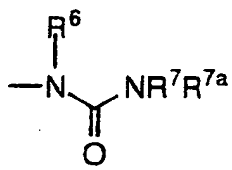
,

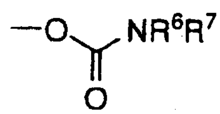
wherein the substituted group is substituted with one or more of:

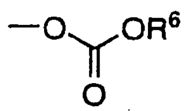
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^6, $S(O)R^6$, SO_2R^6,

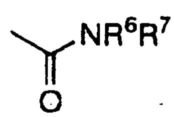
5) $-NR^6R^7$,

6)  ,

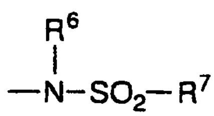
7)  ,

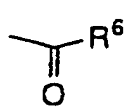
8)  ,

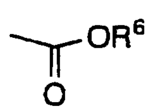
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  , or

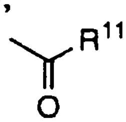
14)  ; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -N(COR^{10})- ;

R^4 and R^5 are independently selected from H and CH_3;

and any two of R^2, R^3, R^4 and R^5 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,

f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-$C(NH)$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

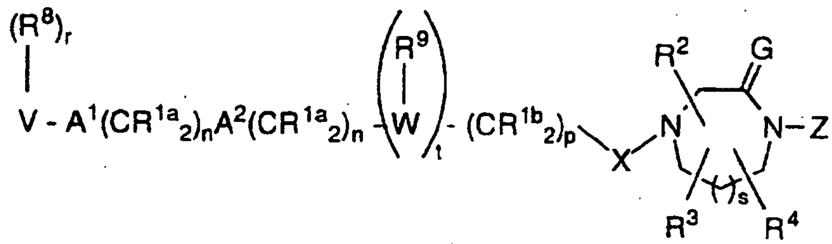
X is -CH_2-, -C(=O)-, or -$S(=O)_m$-;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$,. or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1; and
u is 4 or 5;

with respect to formula (II-b):



(II-b)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, R^{7a}, u, R^8, A^1, A^2, V, W, X, n, p, r, s, t and u are as defined above with respect to formula (II-a);

R^4 is selected from H and CH_3;

and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^9 is selected from:

a) hydrogen,
b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

G is H_2 or O;

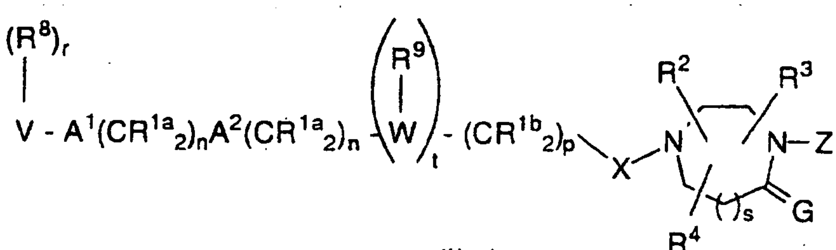
Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,

b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) aryl or heterocycle,
e) HO,
f) $-S(O)_mR^6$, or
g) $-C(O)NR^6R^7$,

2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

with respect to formula (II-c):



(II-c)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, u, R^{7a}, R^8, A^1, A^2, V, W, X, n, r and t are as defined above with respect to formula (II-a);

R^4 is selected from H and CH_3;

and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

G is O;

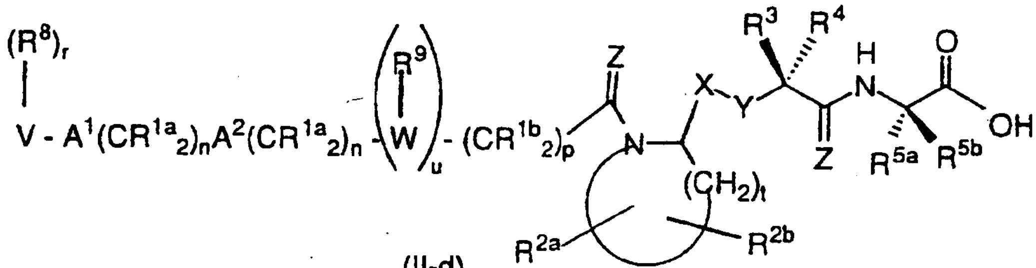
Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

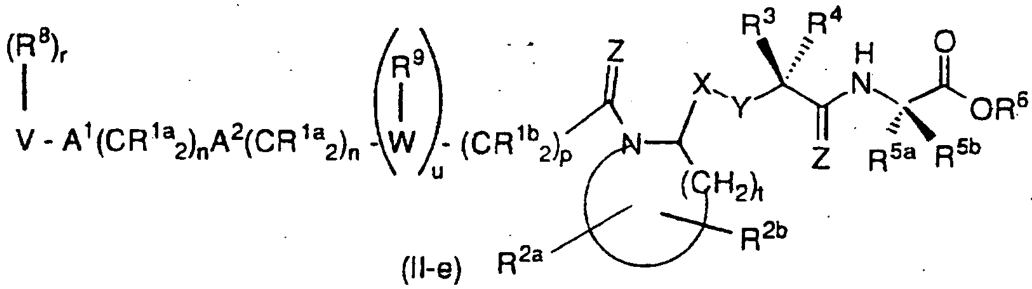
and

s is 1;

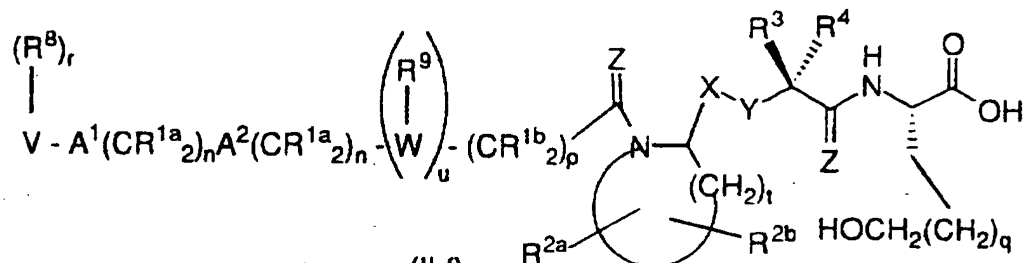
(b) a compound represented by formula (II-d) through (II-g):



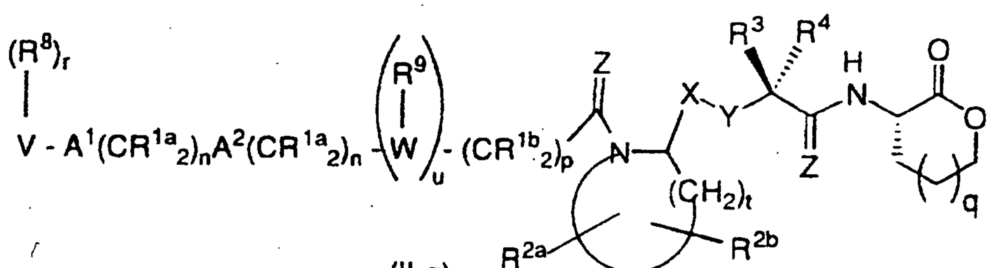
(II-d)



(II-e)

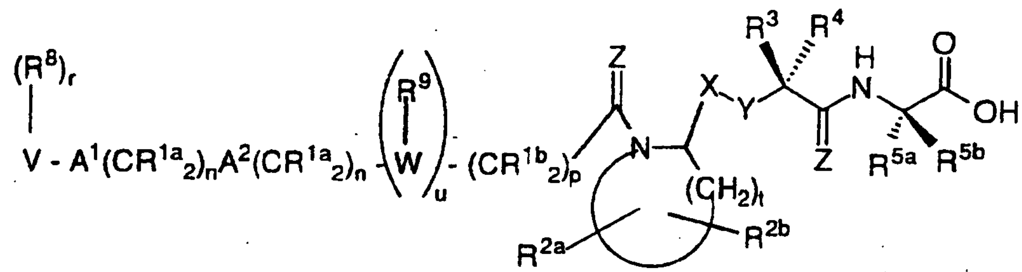


(II-f)



(II-g)

wherein with respect to formula (II-d):



(II-d)

or a pharmaceutically acceptable salt thereof,

R^{11}, V, W, m, n, p and r are as defined above with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^{2a} and R^{2b} are independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3,

$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone, and

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3- C_{10} cycloalkyl; or

R^3 and R^4 are combined to form - $(CH_2)_s$ - ;

R^{5a} and R^{5b} are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,

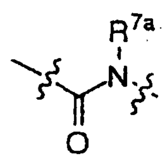
wherein the substituent is selected from F, Cl, Br, CF_3, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-,

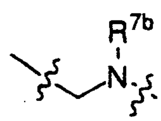
$R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl,

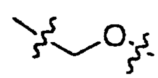
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

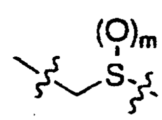
R^{5a} and R^{5b} are combined to form - $(CH_2)_s$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -N(COR^{10})- ;

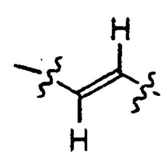
X-Y is

a)  ,

b)  ,

c)  ,

d)  ,

e)  , or

f) $-CH_2-CH_2-$;

R^{7a} is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,

c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^{7b} is selected from
a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl,
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl,
f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl, and
g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^8 is independently selected from:
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6

alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-C(NH)-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

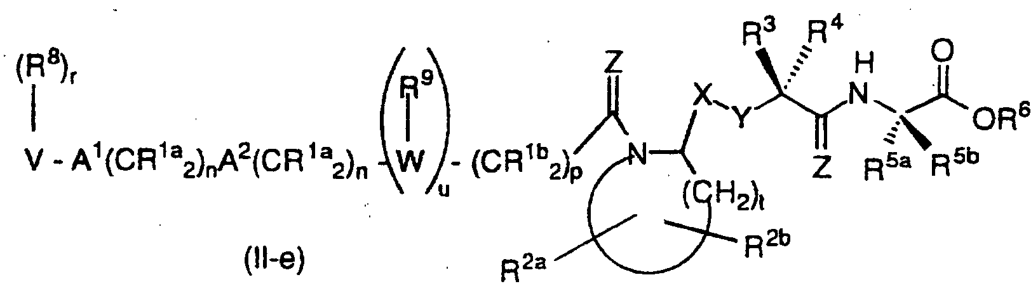
R^{10} is independently selected from H, C_1-C_6 alkyl, benzyl, substituted aryl and C_1-C_6 alkyl substituted with substituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

Z is independently H_2 or O;

s is 4 or 5;
t is 3, 4 or 5; and
u is 0 or 1;

with respect to formula (II-e):



(II-e)

or a pharmaceutically acceptable salt thereof,

R^{11}, W, m, n, p and r are as defined above with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^{2a} and R^{2b} are independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2,

$(R^{10})_2N\text{-}C(NR^{10})\text{-}$, $R^{10}C(O)\text{-}$, $R^{10}OC(O)\text{-}$, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}\text{-}$, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O\text{-}$, $R^{11}S(O)_m\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, CN, $(R^{10})_2N\text{-}C(NR^{10})\text{-}$, $R^{10}C(O)\text{-}$, $R^{10}OC(O)\text{-}$, N_3, $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}\text{-}$ and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^3 and R^4 are combined to form $-(CH_2)_s-$;

R^{5a} and R^{5b} are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,

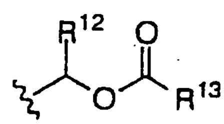
wherein the substituent is selected from F, Cl, Br, CF_3, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form - $(CH_2)_s$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^6 is

a) substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_5-C_8 cycloalkyl, or substituted or unsubstituted cyclic amine, wherein the substituted alkyl, cycloalkyl or cyclic amine is substituted with 1 or 2 substituents independently selected from:
   1) C_1-C_6 alkyl,
   2) aryl,
   3) heterocycle,
   4) -$N(R^{11})_2$,
   5) -OR^{10}, or

b) 

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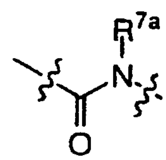
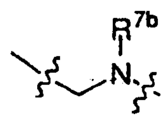
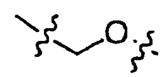
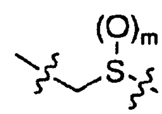
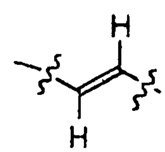
X-Y is

a)  ,

b)  ,

c)  ,

d)  ,

e)  , or

f) $-CH_2-CH_2-$;

R^{7a} is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^{7b} is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,

c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl,
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl,
f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl, and
g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^8 is independently selected from:
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-$C(NH)$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:
a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F,

Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from H, C_1-C_6 alkyl, benzyl, substituted aryl and C_1-C_6 alkyl substituted with substituted aryl;

R^{12} is hydrogen or C_1-C_6 alkyl;

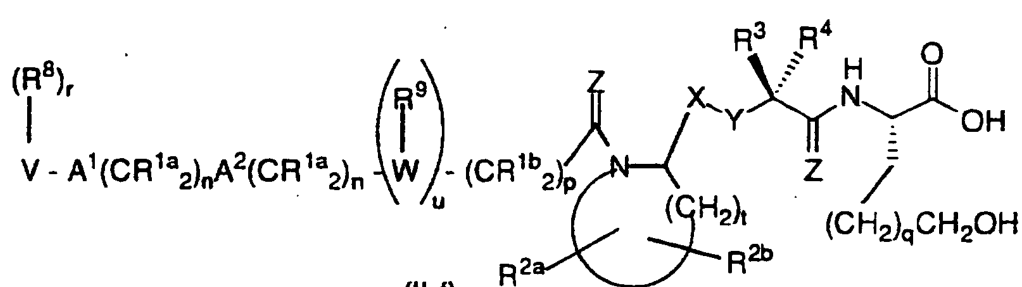
R^{13} is C_1-C_6 alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

Z is independently H_2 or O;

s is 4 or 5;
t is 3, 4 or 5; and
u is 0 or 1;

with respect to formula (II-f):



(II-f)

or a pharmaceutically acceptable salt thereof,

R^{11}, V, W, m, n, p and r are as defined above with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^{2a} and R^{2b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone, and

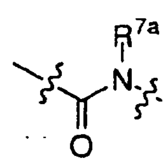
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

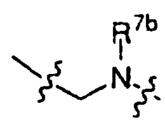
wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

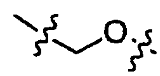
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

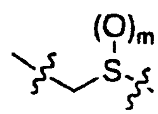
R^3 and R^4 are combined to form - $(CH_2)_s$ - ;

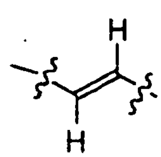
X-Y is

a)  ,

b)  ,

c)  ,

d)  ,

e)  , or

f) -CH_2-CH_2- ;

R^{7a} is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^{7b} is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl,
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl,
f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl, and
g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-,

$R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-C(NH)-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from H, C_1-C_6 alkyl, benzyl, substituted aryl and C_1-C_6 alkyl substituted with substituted aryl;

R^{12} is hydrogen or C_1-C_6 alkyl;

R^{13} is C_1-C_6 alkyl;

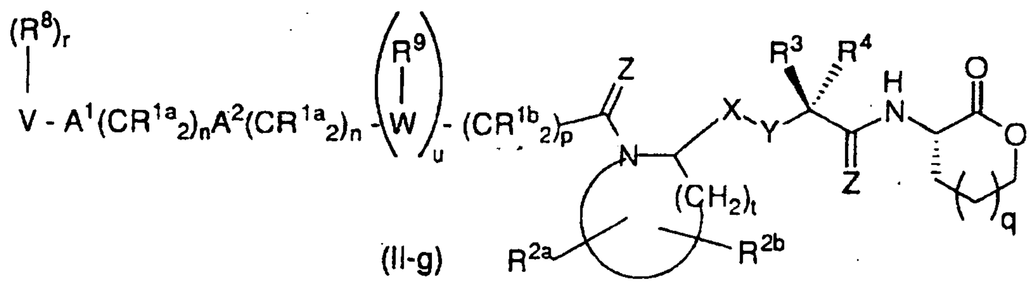
A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, or S(O)$_m$;

Z is independently H_2 or O;

q is 0, 1 or 2;
s is 4 or 5;

t is	3, 4 or 5; and
u is	0 or 1;

with respect to formula (II-g):



(II-g)

or a pharmaceutically acceptable salt thereof,

R^{11}, V, W, m, n, p and r are as previously defined with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R2a and R2b are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

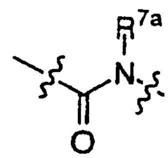
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,

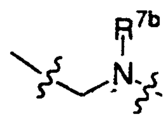
wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

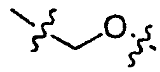
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

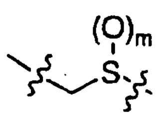
R^3 and R^4 are combined to form - $(CH_2)_s$ - ;

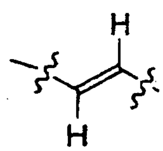
X-Y is

a)  ,

b)  ,

c)  ,

d)  ,

e)  , or

f) $-CH_2-CH_2-$;

R^{7a} is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^{7b} is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,

d) unsubstituted or substituted C_3-C_{10} cycloalkyl,

e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl,

f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl, and

g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-$C(NH)$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from H, C_1-C_6 alkyl, benzyl, substituted aryl and C_1-C_6 alkyl substituted with substituted aryl;

R^{12} is hydrogen or C_1-C_6 alkyl;

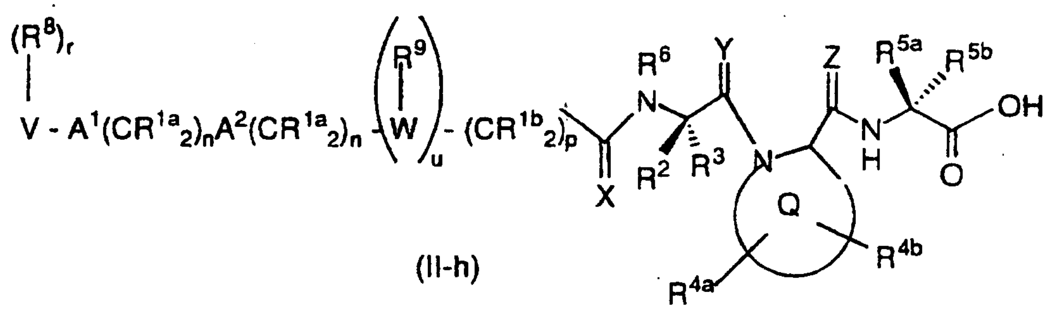
R^{13} is C_1-C_6 alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

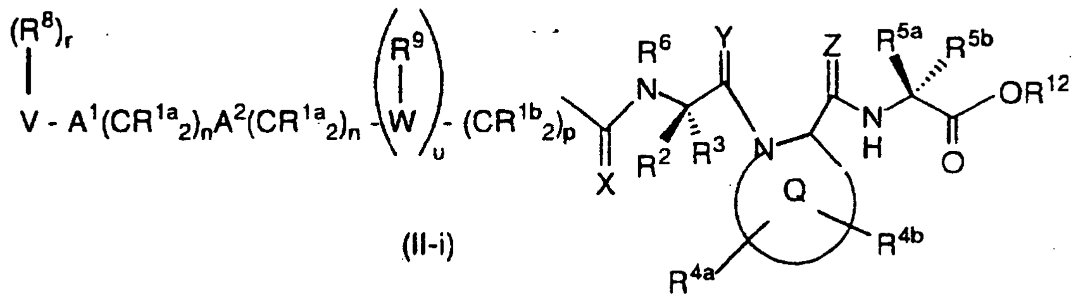
Z is independently H_2 or O;

q is	0, 1 or 2;
s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

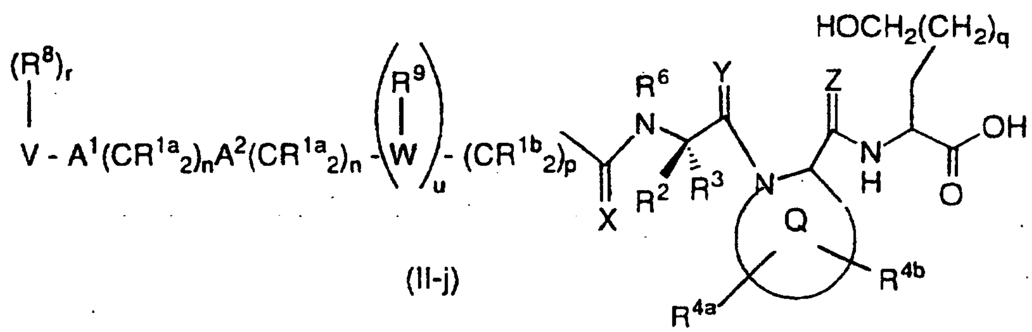
(c) a compound represented by formula (II-h) through (II-k):



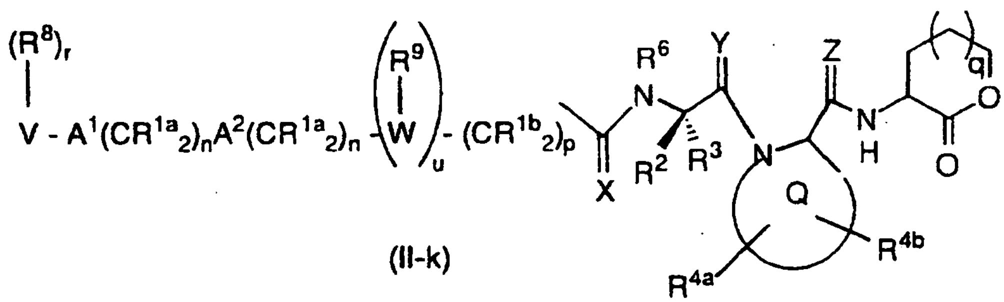
(II-h)



(II-i)

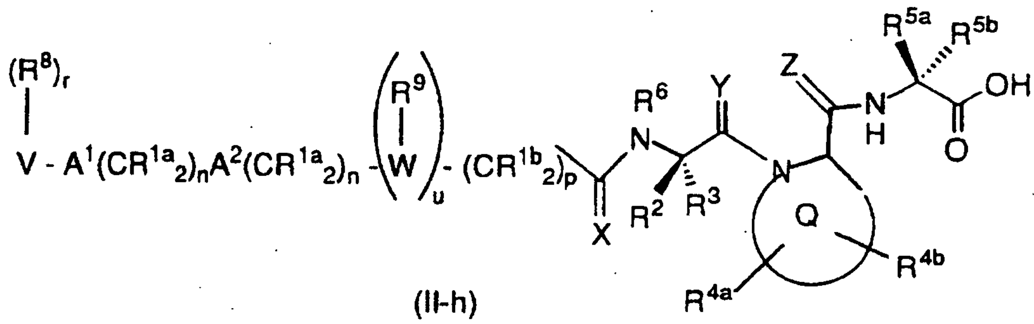


(II-j)



(II-k)

wherein with respect to formula (II-h):



(II-h)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as previously defined with respect to formula (II-a);

R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,

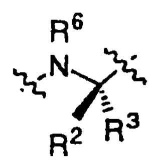
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone, and

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,
   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

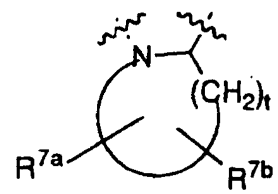
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form - $(CH_2)_s$ - ; or

R^2 or R^3 are combined with R^6 to form a ring such that



is



;

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^{5a} and R^{5b} are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl,

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form - $(CH_2)_s$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -N(COR^{10})- ;

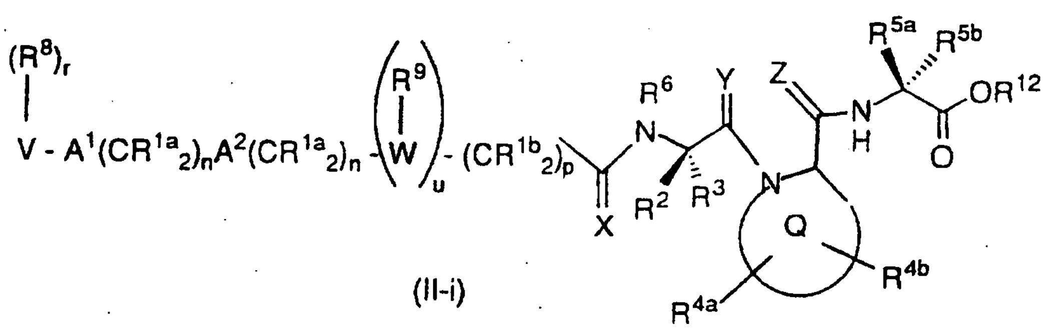
R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

with respect to formula (II-i):



(II-i)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as previously defined with respect to formula (II-a);

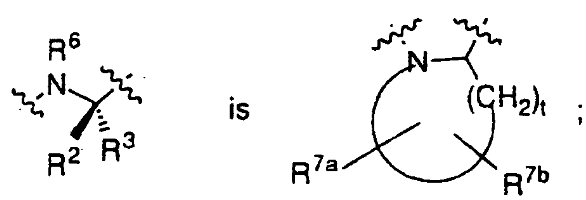
R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone, and
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,
   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form - $(CH_2)_s$ - ; or

R^2 or R^3 are combined with R^6 to form a ring such that



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^{5a} and R^{5b} are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl,

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form - $(CH_2)_s$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

R^{12} is

a) substituted or unsubstituted C_1-C_8 alkyl or substituted or unsubstituted C_5-C_8 cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:

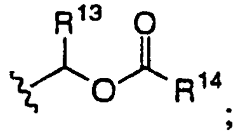
1) aryl,

2) heterocycle,

3) -$N(R^{11})_2$,

4) -OR^{10}, or

b)



R13 is independently selected from hydrogen and C_1-C_6 alkyl;

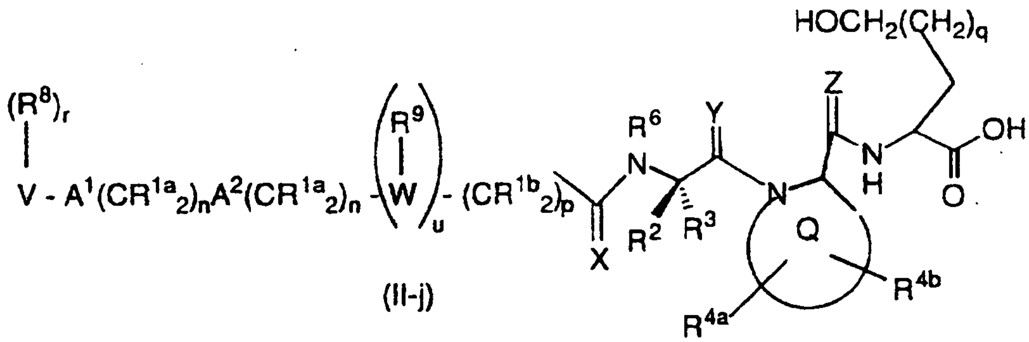
R^{14} is independently selected from C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

s is 4 or 5;
t is 3, 4 or 5; and
u is 0 or 1;

with respect to formula (II-j):



(II-j)

or a pharmaceutically acceptable salt thereof,

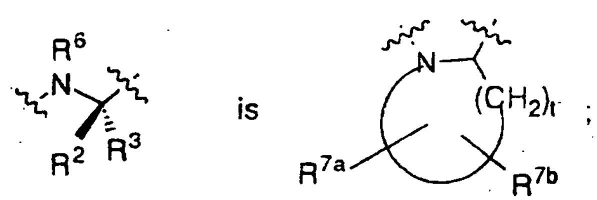
R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as previously defined with respect to formula (II-a);

R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone, and
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,
   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form $-(CH_2)_s-$; or

R^2 or R^3 are combined with R^6 to form a ring such that



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

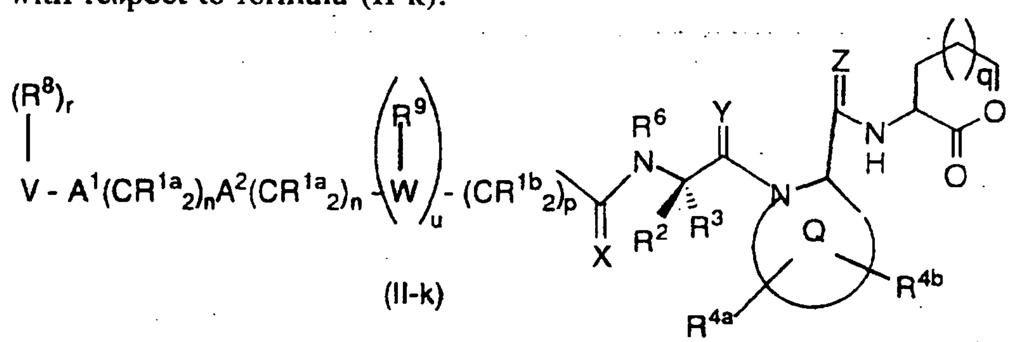
R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

q is	0, 1 or 2;
s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

with respect to formula (II-k):



(II-k)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p, and r are as defined above with respect to formula (II-a);

R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,

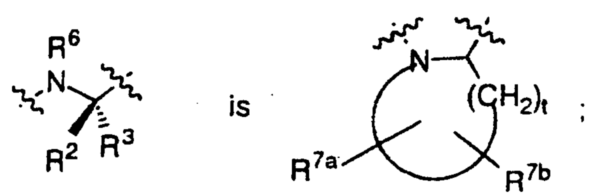
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone, and

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,
   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form - $(CH_2)_s$ - ; or

R^2 or R^3 are combined with R^6 to form a ring such that



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

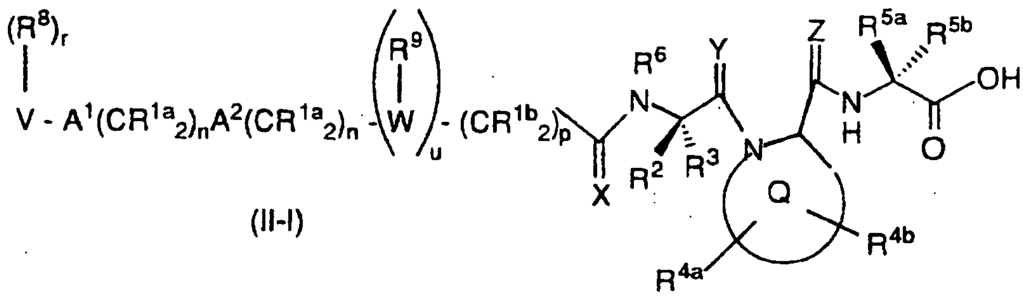
R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

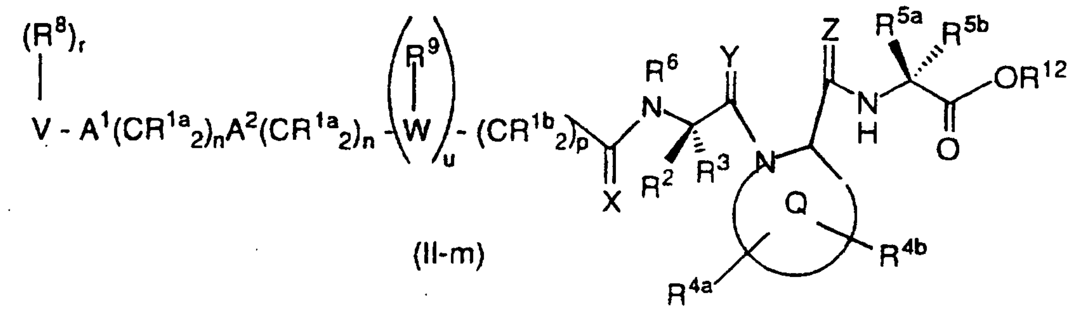
X, Y and Z are independently H_2 or O;

q is	0, 1 or 2;
s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

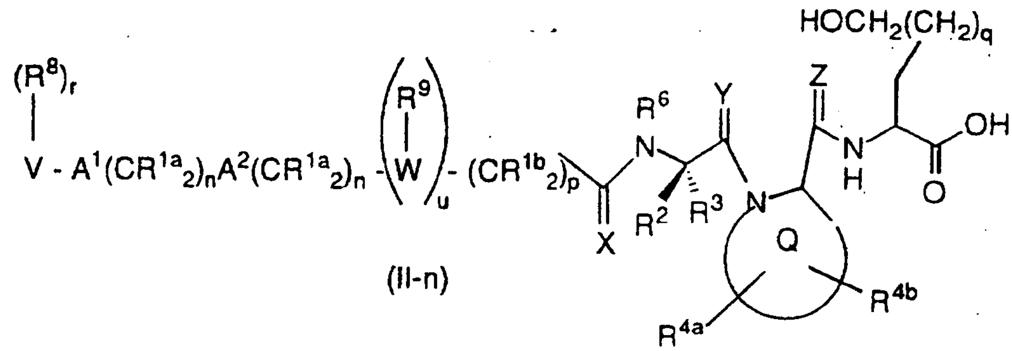
and (d) a compound represented by formula (II-l) through (II-o):



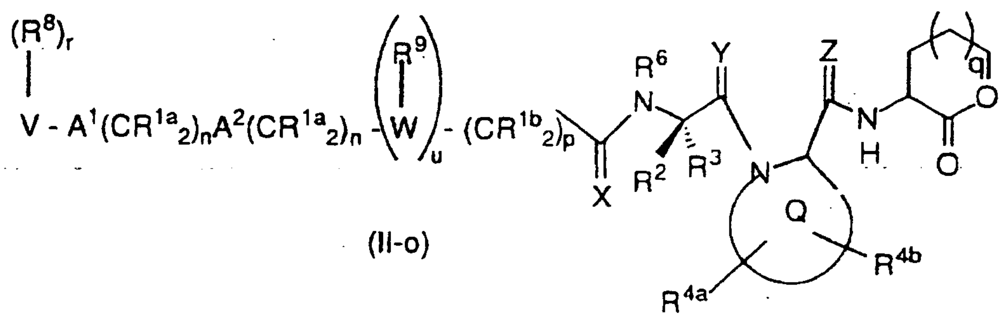
(II-l)



(II-m)

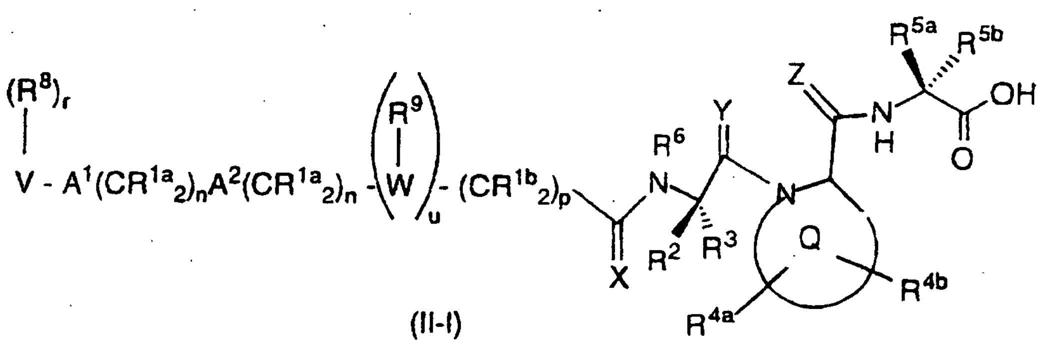


(II-n)



(II-o)

wherein with respect to formula (II-l):



(II-l)

or a pharmaceutically acceptable salt thereof:

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as defined above with respect to formula (II-a);

R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

   i) methionine sulfoxide, or

   ii) methionine sulfone, and

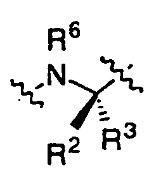
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form - $(CH_2)_s$ - ; or

R^2 or R^3 are combined with R^6 to form a ring such that



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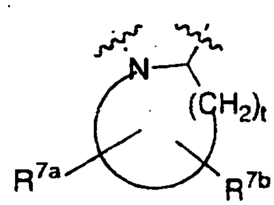


;

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^{5a} and R^{5b} are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl,

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form - $(CH_2)_s$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

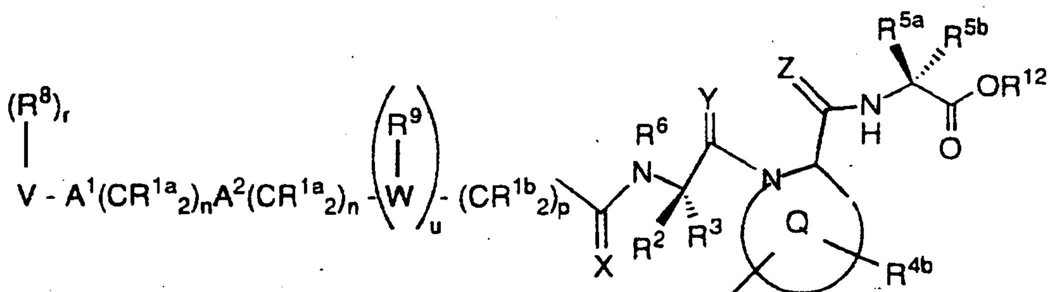
R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

s is 4 or 5;
t is 3, 4 or 5; and
u is 0 or 1;

with respect to formula (II-m):



(II-m)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as defined above with respect to formula (II-a);

R^2 and R^3 are independently selected from:

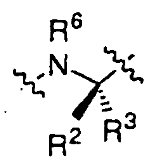
a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone, and
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N\text{-}C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or .

R^2 and R^3 are combined to form - $(CH_2)_s$ - ; or

R^2 or R^3 are combined with R^6 to form a ring such that



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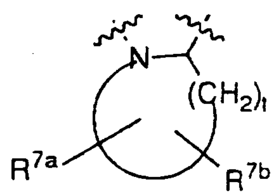


;

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N\text{-}C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N\text{-}C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^{5a} and R^{5b} are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:
 i) methionine sulfoxide, or
 ii) methionine sulfone,

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,
 wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl,

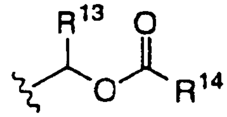
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form - $(CH_2)_s$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

R^{12} is

a) substituted or unsubstituted C_1-C_8 alkyl or substituted or unsubstituted C_5-C_8 cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:
 1) aryl,
 2) heterocycle,
 3) -$N(R^{11})_2$,
 4) -OR^{10}, or

b) 
;

R^{13} is independently selected from hydrogen and C_1-C_6 alkyl;

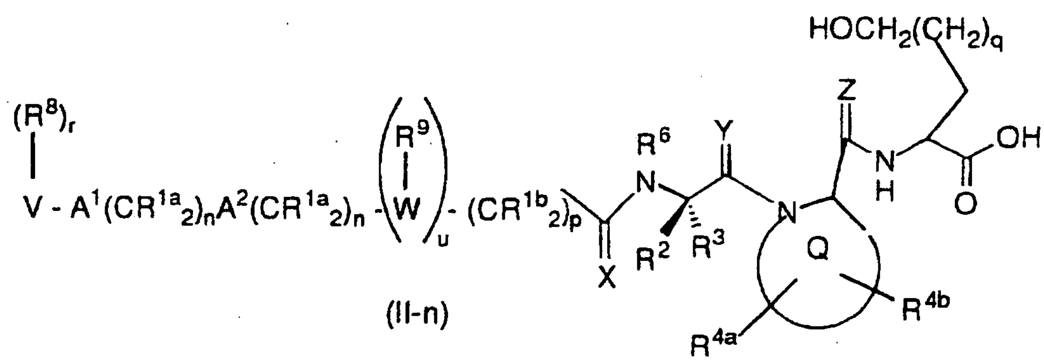
R^{14} is independently selected from C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

s is 4 or 5;
t is 3, 4 or 5; and
u is 0 or 1;

with respect to formula (II-n):



(II-n)

or a pharmaceutically acceptable salt thereof:

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as defined above with respect to formula (II-a);

R^2 and R^3 are independently selected from:

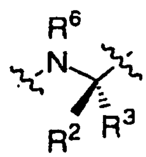
a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone, and
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form - $(CH_2)_s$ - ; or

R^2 or R^3 are combined with R^6 to form a ring such that



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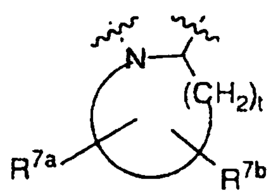


;

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

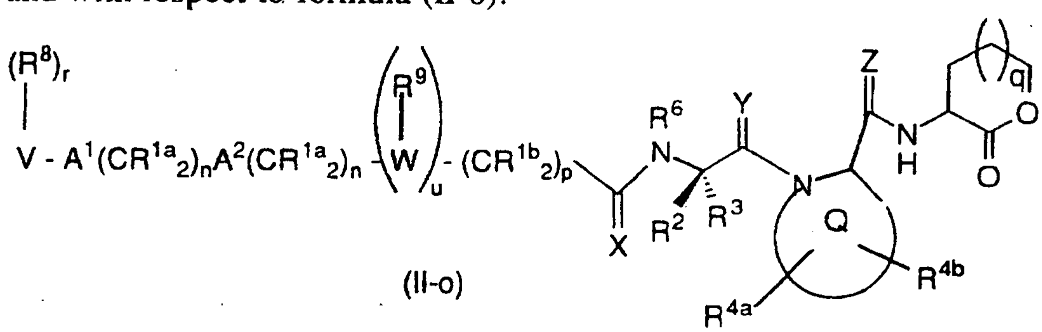
R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C4-C9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C5-C7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

q is	0, 1 or 2;
s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

and with respect to formula (II-o):



(II-o)

or a pharmaceutically acceptable salt thereof:

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as defined above with respect to formula (II-a);

R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

   i) methionine sulfoxide, or

   ii) methionine sulfone, and

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

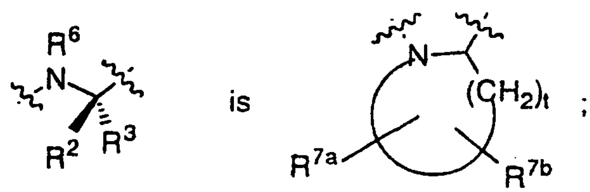
   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-,

CN, $(R^{10})_2N\text{-}C(NR^{10})\text{-}$, $R^{10}C(O)\text{-}$, $R^{10}OC(O)\text{-}$, N_3, $\text{-}N(R^{10})_2$, $R^{11}OC(O)NR^{10}\text{-}$ and $C_1\text{-}C_{20}$ alkyl, and

d) $C_1\text{-}C_6$ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and $C_3\text{-}C_{10}$ cycloalkyl; or

R^2 and R^3 are combined to form $\text{-}(CH_2)_s\text{-}$; or

R^2 or R^3 are combined with R^6 to form a ring such that



R4a, R4b, R7a and R7b are independently selected from:

a) hydrogen,
b) $C_1\text{-}C_6$ alkyl unsubstituted or substituted by alkenyl, $R^{10}O\text{-}$, $R^{11}S(O)_m\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, CN, N_3, $(R^{10})_2N\text{-}C(NR^{10})\text{-}$, $R^{10}C(O)\text{-}$, $R^{10}OC(O)\text{-}$, $\text{-}N(R^{10})_2$, or $R^{11}OC(O)NR^{10}\text{-}$,
c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O\text{-}$, $R^{11}S(O)_m\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, CN, NO_2, $(R^{10})_2N\text{-}C(NR^{10})\text{-}$, $R^{10}C(O)\text{-}$, $R^{10}OC(O)\text{-}$, N_3, $\text{-}N(R^{10})_2$ or $R^{11}OC(O)NR^{10}\text{-}$, and
d) $C_1\text{-}C_6$ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and $C_3\text{-}C_{10}$ cycloalkyl;

R^6 is independently selected from hydrogen or $C_1\text{-}C_6$ alkyl;

Q is a substituted or unsubstituted nitrogen-containing $C_4\text{-}C_9$ mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a $C_5\text{-}C_7$ saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

q is	0, 1 or 2;
s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1.

Specific compounds which antagonize Raf include the following:
4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

4-[4-fluorophenyl)-3-pyridin-yl-1H-imidazol-2-yl]-1-acetyl-piperidine;

3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

3-[4-fluorophenyl)-3-pyridin-yl-1H-imidazol-2-yl]-1-acetyl-piperidine; and

4-benzyl-[4-(4-fluorophenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester.
4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-benzyl-piperidine;

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-ethyl-piperidine;

4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;

4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

2-(4-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-butyl)-isoindole-1,3-dione;

2-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-pentyl)-isoindole-1,3-dione;

2-(6-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-hexyl)-isoindole-1,3-dione;

4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-benzyl-piperidine;

2-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-pentyl)-2,3-dihydro-isoindol-1-one ditrifluoroacetic acid salt;

4-(4-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-ethyl)-pyridine;

2-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-pentyl)-1,1-dioxobenzo[d]isothiazol-3-one;

2-(4-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-butyl)-1,1-dioxobenzo[d]isothiazol-3-one;

2-amino-1-{5-[4-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-ethanone dihydrochloride;

4-[5-(3-hydroxyphenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidine:

3-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1-methyl-piperidine;

4-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-1,4-dimethyl-piperidine;

4-benzyl-[4-(4-fluorophenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-piperidine-1-carboxylic acid *tert*-butyl ester;

4-benzyl-[4-(4-fluorophenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-piperidine;

4-{5-(3,4-dichlorophenyl)-2-[1-(2-phenylethyl)-piperidin-4-yl]-1H-imidazol-4-yl}-pyridine;

4-{5-(3,4-dichlorophenyl)-2-[1-(3-phenylpropyl)-piperidin-4-yl]-1H-imidazol-4-yl}-pyridine;

2-(6-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-hexyl)-1,1-dioxobenzo[d]isothiazol-3-one;

2-(3-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-propyl)-1,1-dioxobenzo[d]isothiazol-3-one;

4-(5-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl-methyl}-imidazol-1-yl-methyl)-benzonitrile;

4-[2-[1-(4-benzyloxybenzyl)-piperidin-4-yl-5-(3,4-dichlorophenyl)-1H-imidazol-4-yl-pyridine;

2-(3-{4-[5-(3,4-dichlorophenyl)-4-pyridin-4-yl-1H-imidazol-2-yl]-piperidin-1-yl}-propyl)-isoindole-1,3-dione;

4-[4-(4-fluorophenyl)-5-(4-pyridyl)imidazol-2-yl]benzamidoxime;

4-(1-naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

4-(1-naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;

4-(2-naphthyl)-2-(4-methylthiophenyl)-5-(4-pyridyl)imidazole;

4-(2-naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(3-thiophenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(2-thiophenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(3-methylthiophenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(3-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(3-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(2-methylthiophenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(2-methylsulfinylphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(2-methylsulfonylphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(4-methoxyphenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-1-methyl-5-(4-pyridyl) imidazole;

4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(4-methylthiophenyl)-1-(N-morpholinopropyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)-1-(N-morpholino-propyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-1-(methylthio-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole;

4-(4-fluorophenyl)-1-(methylsulfinyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole; and

4-(4-fluorophenyl)-1-(methylsulfonyl-1-propyl)-2-([4-N-morpholinomethyl]phenyl)-5-(4-pyridyl)imidazole.

Examples of compounds which antagonize or inhibit farnesyl protein transferase include the following:

2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;

1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine;

1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;

2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;

1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)acetyl]-4-(1-naphthoyl)piperazine;

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)ethyl]-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-3-hydroypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

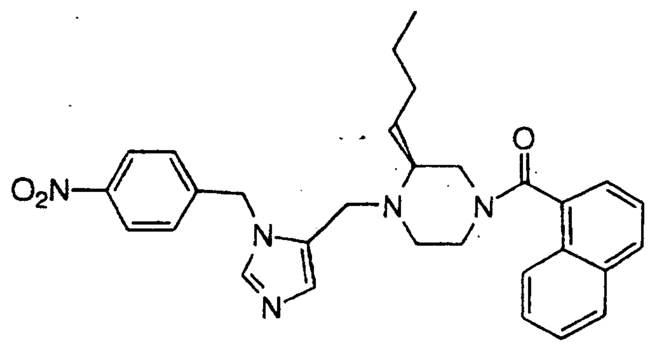
1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;

1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine



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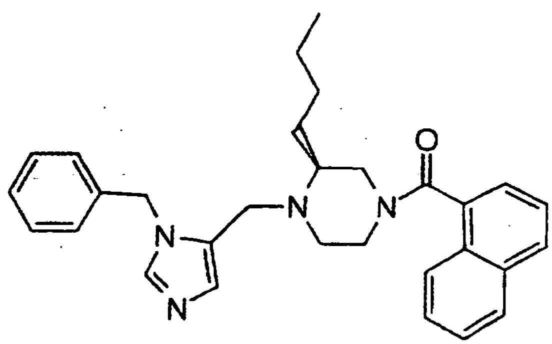
1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine



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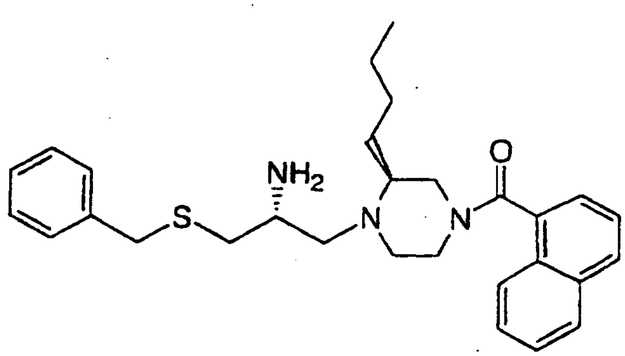
1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine



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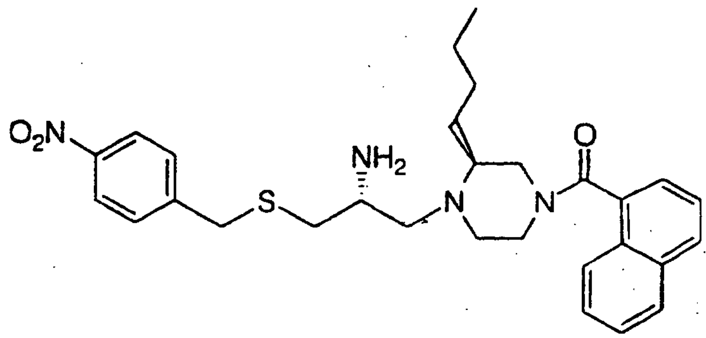
1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine



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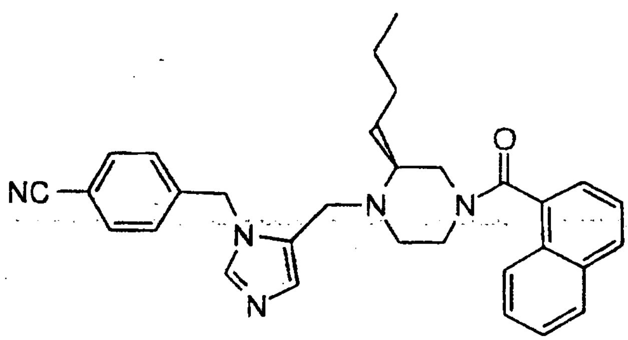
2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine



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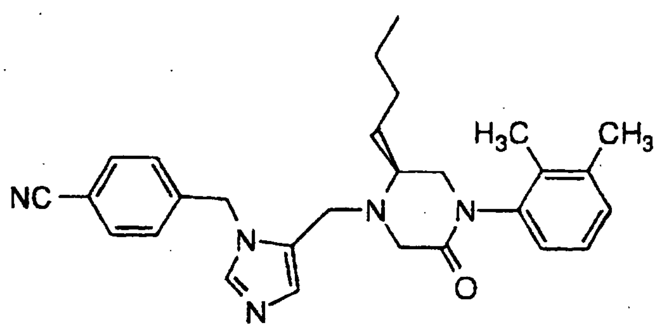
2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one



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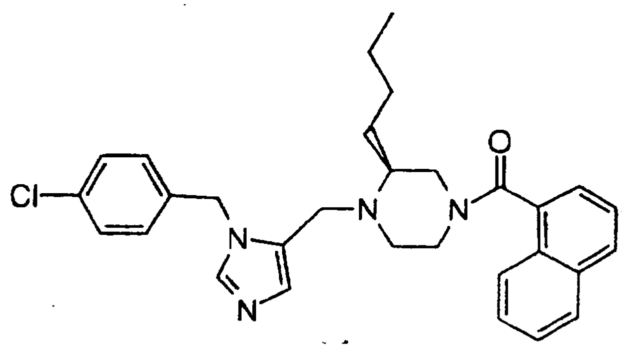
2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine



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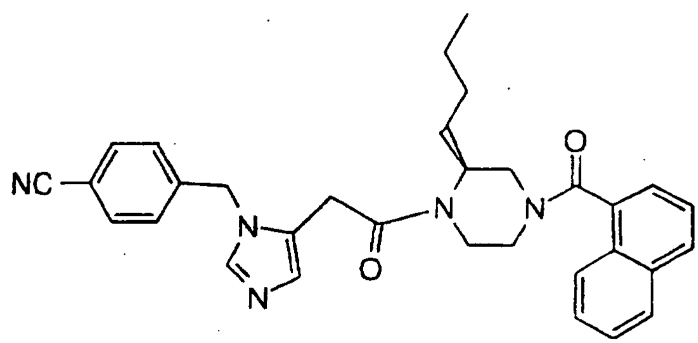
1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine



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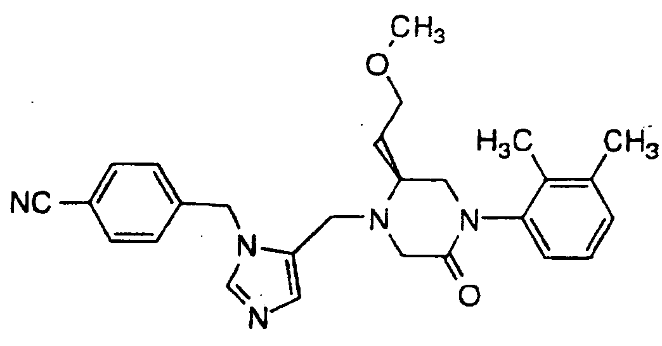
1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one



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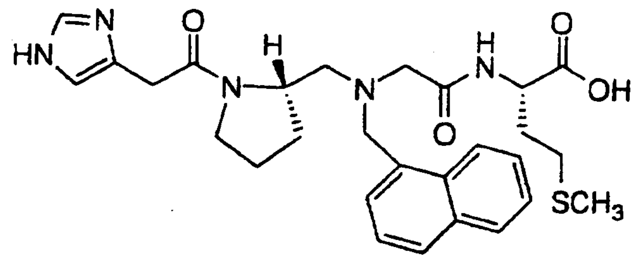
N-[1-(4-Imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycylmethionine



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N-[1-(4-Imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2(S),3-Diaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2(S),3-Diaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(3-Aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-Aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2(S)-Amino-3-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2(S)-Amino-3-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(3-Amino-2(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-Amino-2(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-Glutaminyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(L-Glutaminyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-Histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ;

N-[1-(L-Histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(D-Histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(D-Histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-Pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(L-Pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine isopropyl ester;

2(S)-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(S)-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine sulfone;

2(S)-[1-(2(S)-Pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine sulfone methyl ester;

2(S)-[1-(Pyrid-3-ylcarboxy)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(S)-[1-(Pyrid-3-ylcarboxy)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(R)-{2-[1-(Naphth-2-yl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenylpropionyl-methionine;

2(R)-{2-[1-(Naphth-2-yl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(Pyrid-3-ylmethyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(S)-[1-(Pyrid-3-ylmethyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine sulfone isopropyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine sulfone;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone methyl ester ;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone;

N-[1-(Sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(Sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(N,N-Dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

N-[1-(N,N-Dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(Glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(Glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-Acetylamino-3(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-Acetylamino-3(S)-aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-Amino-3(S)-acetylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

2(S)-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(R)-{2-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester ;

2(R)-{2-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

2(R)-{2-[1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;

2(R)-{2-[1-(4-Nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

2(R)-{2-[1-(4-Methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;

2(R)-{2-[1-(4-Methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

2(R)-{2-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;

2(R)-{2-[1-(4-Cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine methyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine;

N-[1-(Seryl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(D-Alanyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-carbonyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(Isoasparagyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(3-Pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2-Pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(Seryl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(D-Alanyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-carbonyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine ;

N-[1-(Isoasparagyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-Pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-Pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylmethyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-Aminoethyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(2-thienyl)alanine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(trifluoromethyl)alanine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(2(S)-amino-4-acetylamino)butyric acid ;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N,N-dimethyl)glutamine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-methoxybenzyl)glycyl-methionine;

N-[1-(Glycyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-((4-Imidazolyl)methyl-(2S)-pyrrolidinylmethyl)-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(2-thienyl)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N,N-dimethyl)glutamine methyl ester ;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(trifluoromethyl)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(2(S)-amino-4-acetylamino)butyric acid methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

N-[1-(Glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(benzyl)glycyl-methionine methyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine cyclohexyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine benzyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ethyl ester;

N-[1-(Sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(N,N-Dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine (2-pyridylmethyl) ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine (1-glyceryl) ester;

N-[1-L-Prolylpyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-Prolyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1-Morpholinoacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1-Morpholinoacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-Piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-Piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-Piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(3-Piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-Pyridyl(N-methyl)glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-Pyridyl(N-methyl)glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylpropionyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine;

N-[1-(1H-Imidazol-4-ylpropionyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine methyl ester;

N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine;

N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine methyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine cyclohexyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N-methyl)glutamine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N-methyl)glutamine methyl ester ;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-methylcarbonylamino)alanine;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-methylcarbonylamino)alanine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-methylsulfonylamino)alanine;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-methylsulfonylamino)alanine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-propionylamino)alanine ;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-propionylamino)alanine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-pyrrolidinon-1-ylamino)alanine;

N-[1-(1H-Imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-pyrrolidinon-1-ylamino)alanine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine;

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-cyanobenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-cyanobenzyl)glycyl-methionine methyl ester ;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-cyanobenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methylbenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methylbenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-trifluoromethylbenzyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-trifluoromethylbenzyl)glycyl-methionine methyl ester;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylsulfonyl)glycyl-methionine;

N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylsulfonyl)glycyl-methionine methyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 4-N-methylpiperidinyl ester;

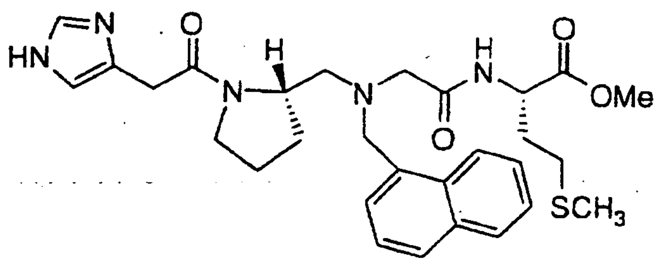
N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine tert-butyl ester;

N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 3-pentyl ester;

N-[1-(4-Pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(11-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(4-Imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester



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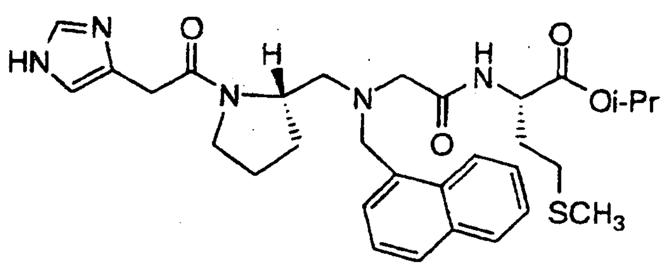
N-[1-(4-Imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester



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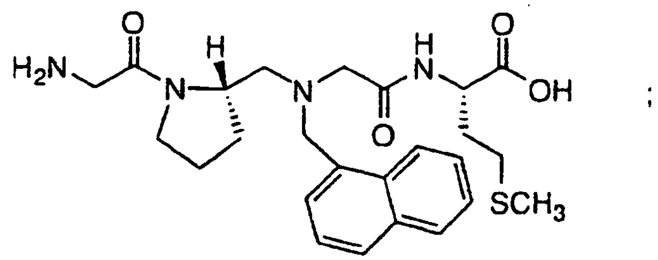

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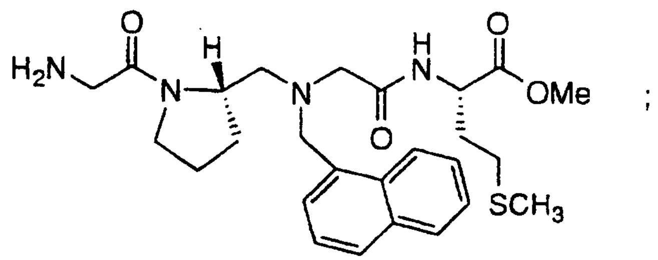

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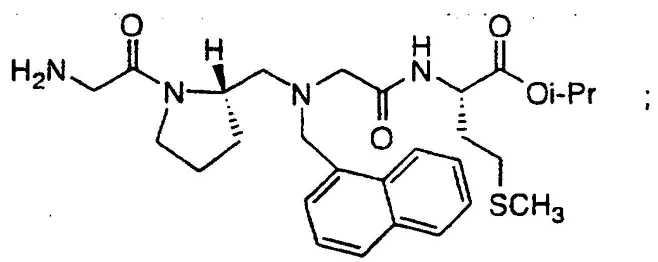

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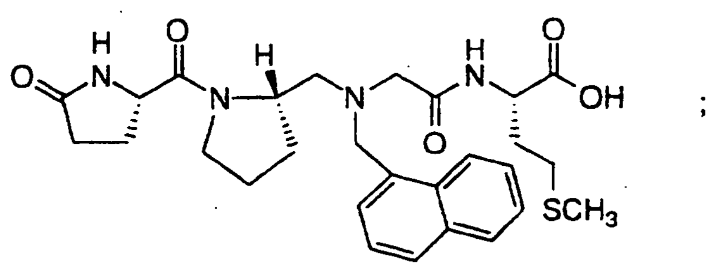
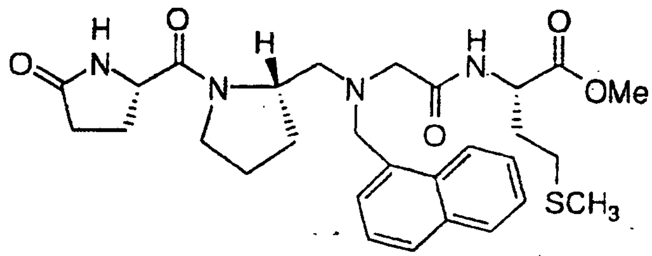


N-[1-(L-Pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester



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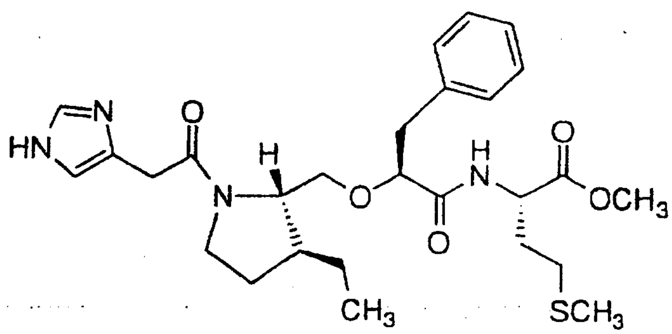
2(S)-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester



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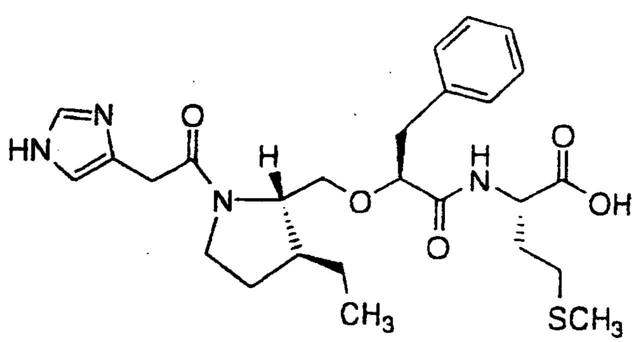
2(S)-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine



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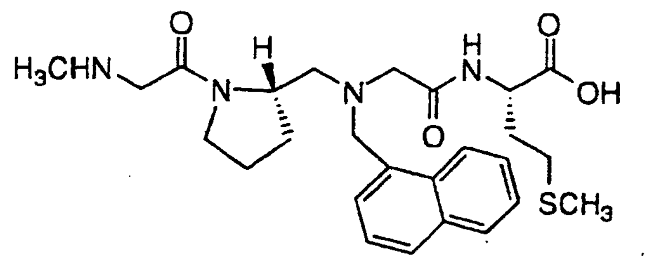
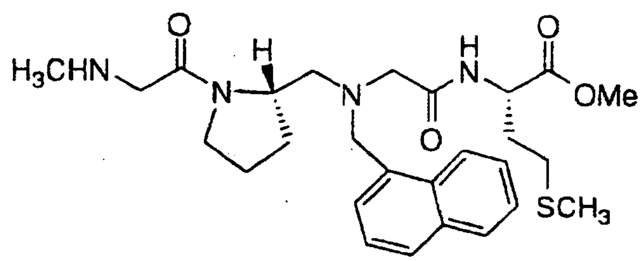
N-[1-(Sarcosyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine


;

N-[1-(Sarcosyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester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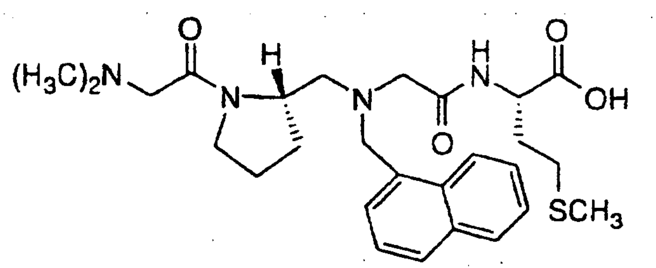
N-[1-(N,N-Dimethylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine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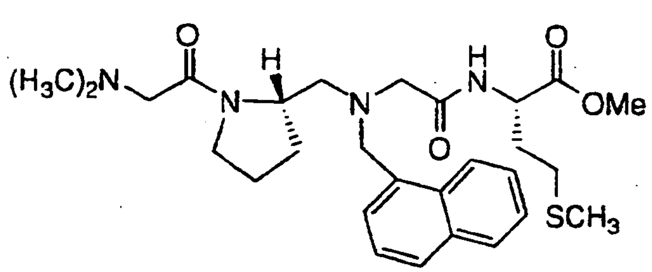
N-[1-(N,N-Dimethylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester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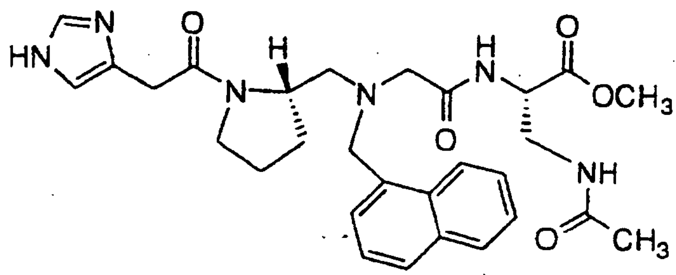
N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine methyl ester



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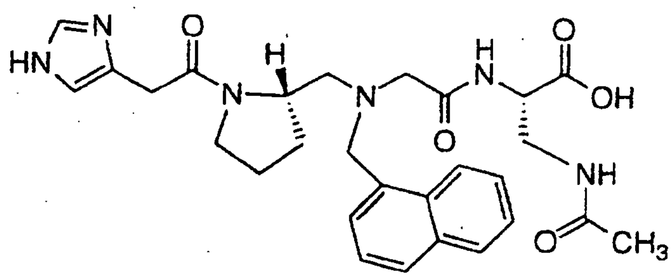
N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine



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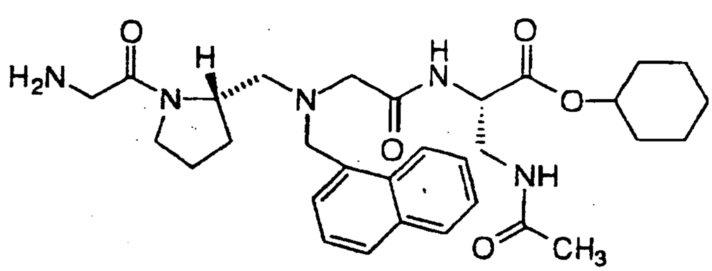
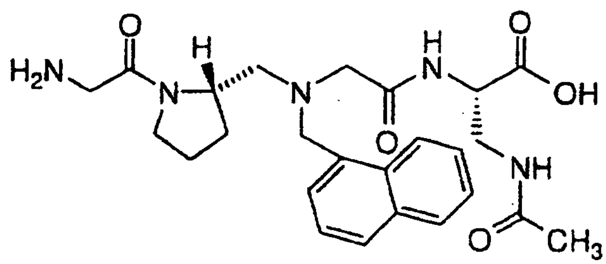
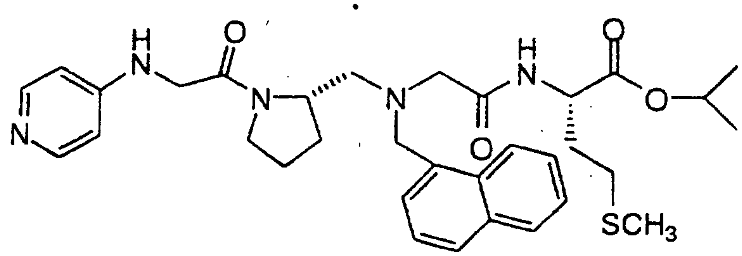
N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine cyclohexyl ester



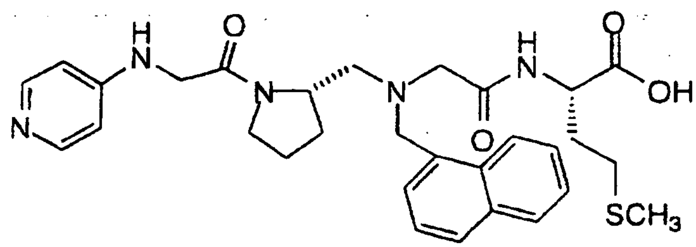
N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine



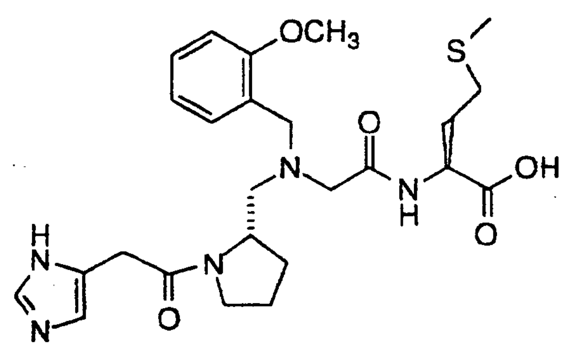
N-[1-(4-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester



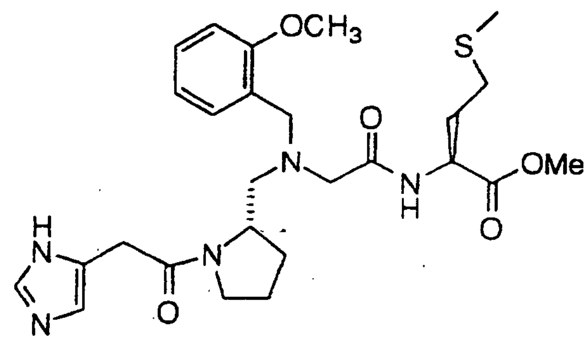
N-[1-(4-Pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine



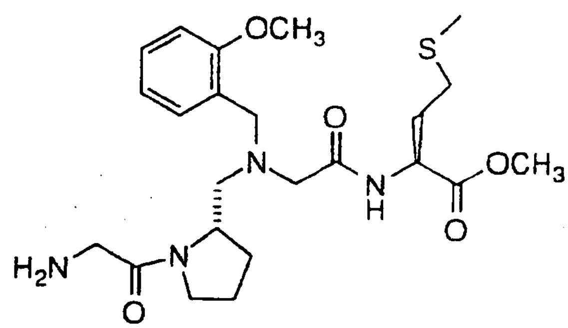
N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine



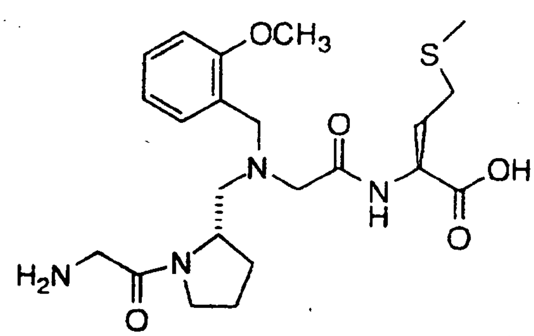
N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester



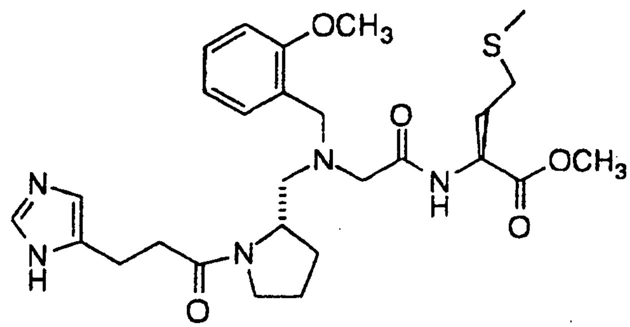
N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester



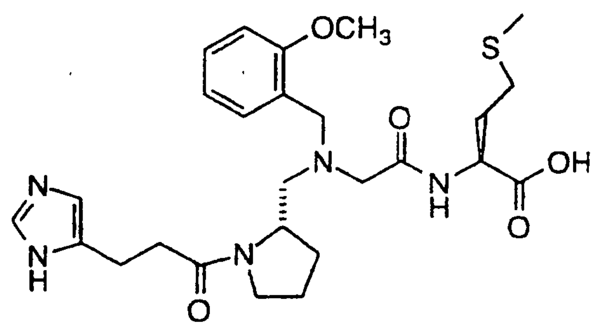
N-[1-(Glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine



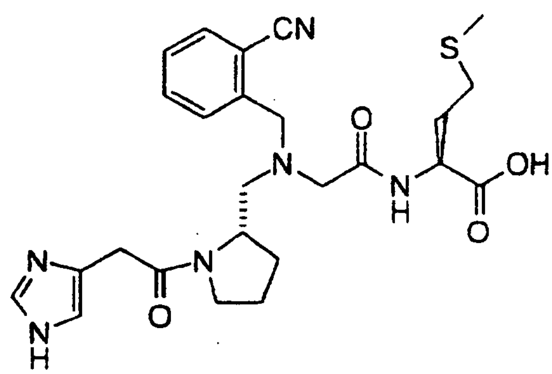
N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester



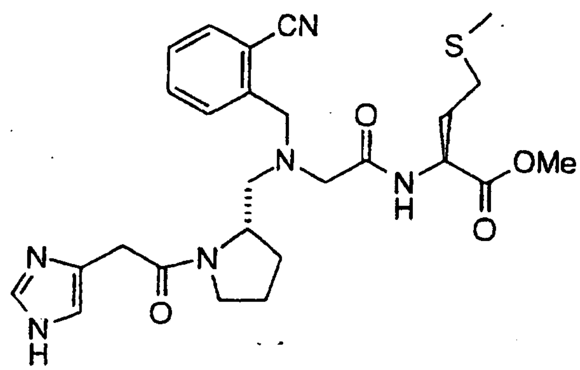
N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine



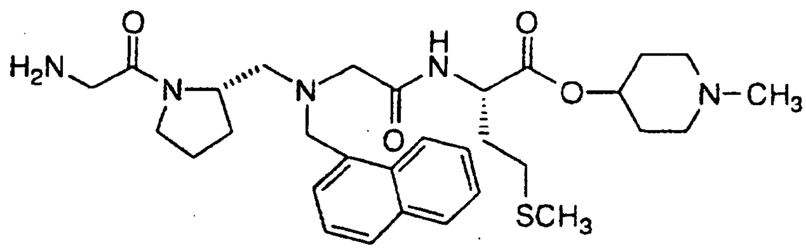
N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine



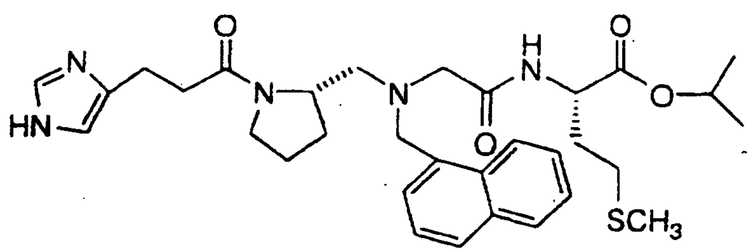
N-[1-(1H-Imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester



N-[1-(Glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 4-N-methylpiperidinyl ester



N-[1-(1H-Imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine isopropyl ester



N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester;

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine;

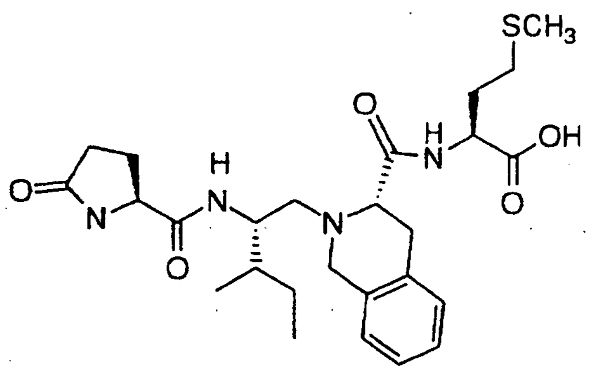
N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine;

N-[1-Glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine methyl ester;

N-[1-Glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine;

N-[L-Pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine



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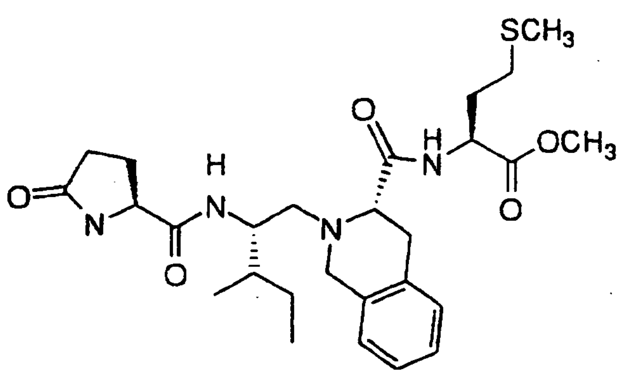
N-[L-Pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester



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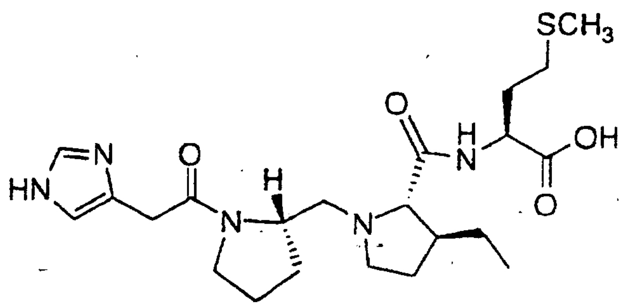
N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine



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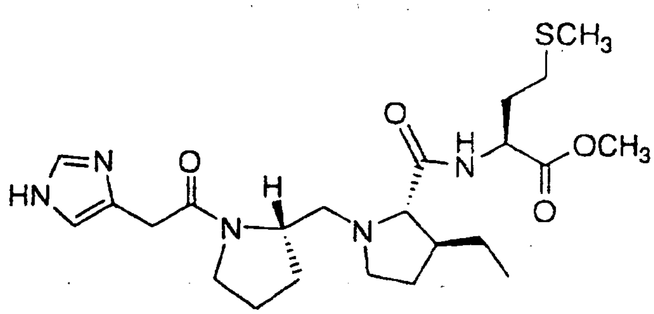
N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S-)ylmethyl]-3(S)-ethylprolyl-methionine methyl ester



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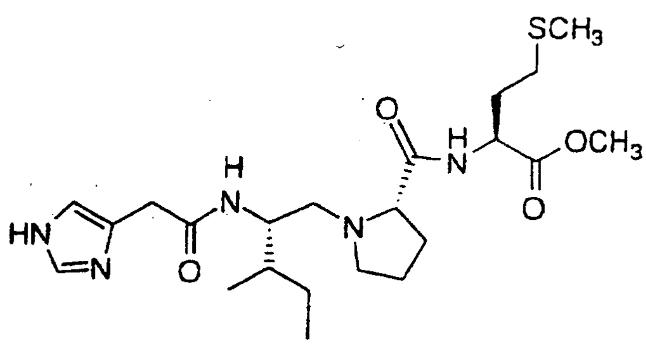
N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester



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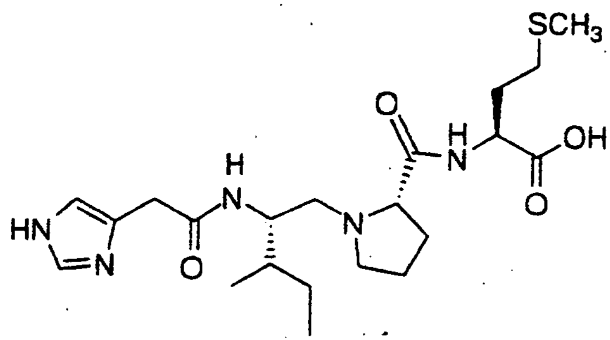
N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine



;

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine

N-[L-Pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester

N-[L-Pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine

N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester

N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine

N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine methyl ester

N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine

N-[1-Glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine methyl ester

N-[1-Glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine
2(S)-Butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine

1-(3-Amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine

2(S)-Butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine

1-[5-(1-Benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine

1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine

1-(3-Acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine

2(S)-Butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine

2(R)-Butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine

2(S)-Butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine

1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine

1-(2(R)-Amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine

2(S)-Benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine

1-(2(R)-Amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine

1-(2(R)-Amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine

2(S)-Butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine

2(S)-Butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)acetyl]-4-(1-naphthoyl)piperazine

2(S)-Butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)ethyl]-4-(1-naphthoyl)piperazine

1-(2(R)-Amino-3-hydroypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine

1-(2(R)-Amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine

1-(2-Amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine

1-(2-Amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine

1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine

2(S)-*n*-Butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one

1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine

2(S)-*n*-Butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine

2(S)-*n*-Butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine

2(S)-*n*-Butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine

2(S)-*n*-Butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine

1-[1-(4-Bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine

2(S)-*n*-Butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine

2(S)-*n*-Butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine

1-[1-(4-Phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine

2(S)-*n*-Butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine

1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine
(N-[1-Cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine

(N-[1-Cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine methyl ester

(N-[1-Cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester
N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester

Compounds which are useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications:

USSN 60/005,059 filed on October 6, 1995;
USSN 60/005,063 filed on October 6, 1995
USSN 60/005,521 filed on October 13, 1995
WO 95/32987 published on 7 December 1995.
U. S. Pat. No. 5,420,245;
European Pat. Publ. 0 618 221 ;
WO 94/26723;
WO 95/08542 ;
WO 95/11917;
WO 95/12612.

U. S. Pat. No. 5,238,922 granted on August 24, 1993; ;

U. S. Pat. No. 5,340,828 granted on August 23, 1994; ;

U. S. Pat. No. 5,352,705 granted on October 4, 1994;

U. S. Pat. No. 5,326,773 granted on July 5, 1994;

USSN 07/968,022 filed on October 29, 1992 ;

USSN 08/968,025 filed on October 29, 1992 and USSN 08/143,943 filed on October 27, 1993 ;

USSN 08/080,028 filed on June 18, 1993 and USSN 08/237,586 filed on May 11, 1994 ;

USSN 08/314,987 filed on September 29, 1994

USSN 08/315,171 filed on September 29, 1994 and PCT WO 96/09836 published on April 4, 1996

USSN 08/315,046 filed on September 29, 1994 ;

USSN 08/315,161 filed on September 29, 1994; USSN 08/399,282 filed on March 6, 1995; USSN 472,077 filed on June 6, 1995, USSN

08/527,972 filed on September 14, 1995 and PCT WO96/10035 published on April 4, 1996

USSN 08/315,151 filed on September 29, 1994 ;

USSN 08/314,974 filed on September 29, 1994 and PCT WO 96/10034 published on April 4, 1996

USSN 08/412,621 filed on March 29, 1995 and USSN 08/448,865 filed on May 24, 1995 ;

USSN 08/413,137 filed on March 29, 1995; ;

USSN 08/412,828 filed on March 29, 1995;

USSN 08/412,829 filed on March 29, 1995; and USSN 08/470,690 filed on June 6, 1995;

USSN 08/412,830 filed on March 29, 1995;

USSN 08/449,038 filed on May 24, 1995; ;

USSN 08/468,160 filed on June 6, 1995; ;

All patents, publications and pending patent applications identified are hereby incorporated by reference.

With regard to the MEK inhibiting compounds, an example of a published MEK inhibiting compound is PD-098059, published in J. Biol. Chem. 270: 27489 (1995) and J. Biol. Chem. 270: 13585 (1995), incorporated herein by reference.

With regard to the farnesyl transferase inhibitors, the term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocycle ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four

heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydro-benzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, pyridonyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolinyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydro-quinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. Preferably, heterocycle is selected from imidazolyl, 2-oxopyrrolidinyl, piperidyl, pyridyl and pyrrolidinyl.

Substituted alkyl, aryl and heteroaryl, and the substituted portions of aralkyl, aralkoxy, heteroaralkyl, heteroaralkoxy and like groups are substituted with from 1-3 groups selected from the group consisting of: halo, hydroxy, cyano, acyl, acylamino, aralkoxy, alkylsulfonyl, arylsulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, alkyl, alkoxy, aryl, aryloxy, aralkoxy, amino, alkylamino, dialkylamino, and sulfonylamino.

With regard to the farnesyl transferase inhibitors, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted with 1 or 2 substitutents selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, N(C_1-C_6 alkyl)$_2$, NO_2, CN, (C_1-C_6 alkyl)O-, -OH, (C_1-C_6 alkyl)S(O)$_m$-, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-,

(C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)-, N_3,(C_1-C_6 alkyl)OC(O)NH- and C_1-C_{20} alkyl.

The terms “heterocycloalkyl" and "heterocyclyl" refer to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, $S(O)_y$ or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms. When three heteroatoms are present in the heterocycle, they are not all linked together.

Examples of heterocyclyls are piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, imidazolinyl, piperazinyl, pyrolidine-2-one, piperidine-2-one and the like.

Acyl as used herein refers to -C(O)C_{1-6} alkyl and -C(O)-aryl.

Acylamino refers to the group -NHC(O)C_{1-6} alkyl and -NHC(O)aryl.

Aralkoxy refers to the group -OC_{1-6} alkylaryl.

Alkylsulfonyl refers to the group -SO_2C_{1-6} alkyl.

Alkylsulfonylamino refers to the group -$NHSO_2C_{1-6}$alkyl.

Arylsulfonylamino refers to the group -$NHSO_2$aryl.

Alkylaminocarbonyl refers to the group -C(O)NHC_{1-6} alkyl.

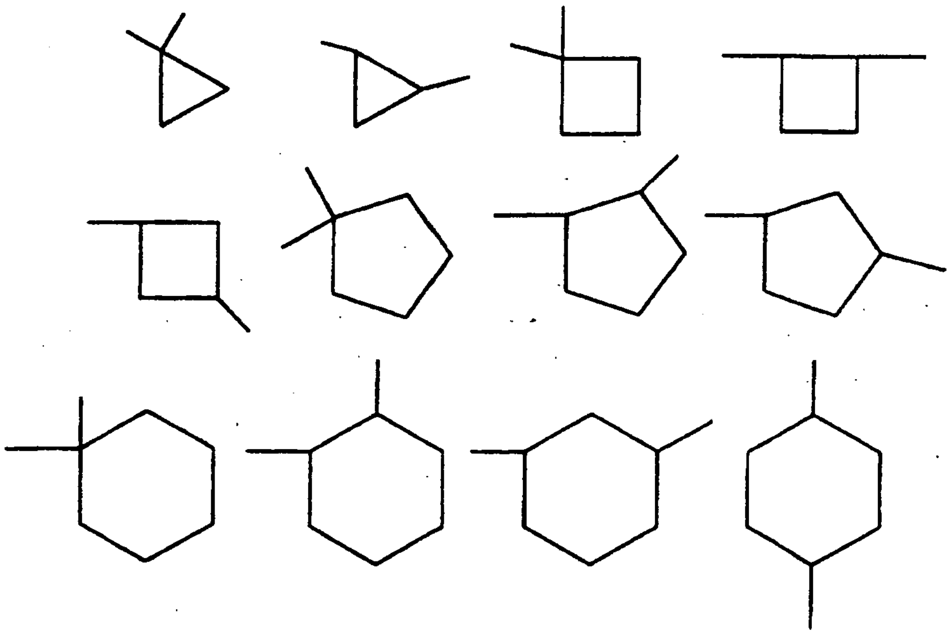
Aryloxy refers to the group -O-aryl.

Aralkoxy refers to the group -O-C_{1-6} alkylaryl.

Sulfonylamino refers to the group -$NHSO_3H$.

Halo means Cl, F, Br and I selected on an independent basis.

Examples of suitable cycloalkylene attachment are as follows:



In each of the patterns of attachment noted above, the ring may also be heterocyclic as defined above.

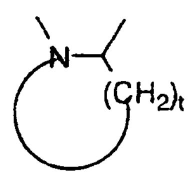
In the present method, amino acids which are disclosed are identified both by conventional 3 letter and single letter abbreviations as indicated below:

Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Asparagine or Aspartic acid	Asx	B
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glutamine or Glutamic acid	Glx	Z
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I

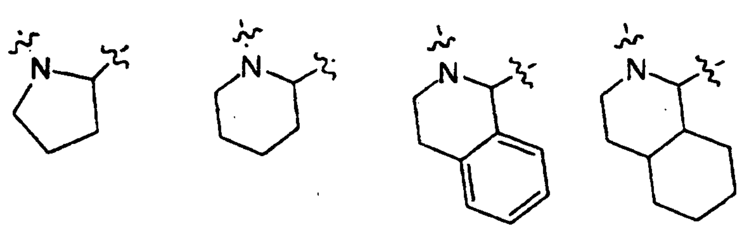
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

The compounds used in the present method may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. Unless otherwise specified, named amino acids are understood to have the natural "L" stereoconfiguration

The following structure:

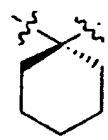


represents a cyclic amine moiety having 5 or 6 members in the ring, such a cyclic amine which may be optionally fused to a phenyl or cyclohexyl ring. Examples of such a cyclic amine moiety include, but are not limited to, the following specific structures:



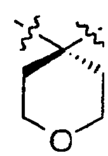
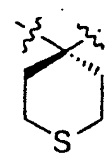
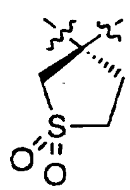
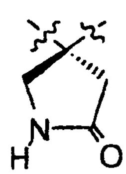
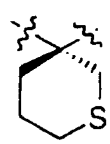
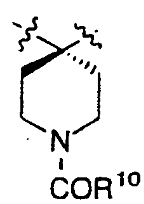
It is also understood that substitution on the cyclic amine moiety by R^{2a} and R^{2b} may be on different carbon atoms or on the same carbon atom.

When R^3 and R^4 are combined to form - $(CH_2)_s$ -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

When R^{5a} and R^{5b} are combined to form - $(CH_2)_s$ -, cyclic moieties as described hereinabove for R^3 and R^4 are formed. In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



It is intended that the definition of any substituent or variable (e.g., R^{10}, Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents -NHH, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth below.

The compounds of formulas (II-a) through (II-k) can be synthesized from their constituent amino acids by conventional peptide synthesis techniques, and the additional methods described below. Standard methods of peptide synthesis are disclosed, for example, in the following works: Schroeder *et al.*, *"The Peptides"*, Vol. I, Academic Press 1965, or Bodanszky *et al.*, *"Peptide Synthesis"*, Interscience Publishers, 1966, or McOmie (ed.) *"Protective Groups in Organic Chemistry"*, Plenum Press, 1973, or Barany *et al.*, *"The Peptides: Analysis, Synthesis, Biology" 2*, Chapter 1, Academic Press, 1980, or Stewart *et al.*, *"Solid Phase Peptide Synthesis"*, Second Edition, Pierce Chemical Company, 1984. Also useful in exemplifying syntheses of specific unnatural amino acid residues are European Pat. Appl. No. 0 350 163 A2 (particularly page 51-52) and J. E. Baldwin *et al. Tetrahedron*, 50:5049-5066 (1994). With regards to the synthesis of instant compounds containing a (β-acetylamino)alanine residue at the C-terminus, use of the commercially available N_{α}-Z-L-2,3-diaminopropionic acid (Fluka) as a starting material is preferred.

Abbreviations used in the description of the chemistry and in the Examples that follow are:

Ac_2O	Acetic anhydride;
Boc	t-Butoxycarbonyl;
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
DMAP	4-Dimethylaminopyridine;
DME	1,2-Dimethoxyethane;
DMF	Dimethylformamide;
EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
HOBT	1-Hydroxybenzotriazole hydrate;
Et_3N	Triethylamine;
EtOAc	Ethyl acetate;
FAB	Fast atom bombardment;
HOOBT	3-Hydroxy-1,2,2-benzotriazin-4(3*H*)-one;
HPLC	High-performance liquid chromatography;
MCPBA	m-Chloroperoxybenzoic acid;

MsCl	Methanesulfonyl chloride;
NaHMDS	Sodium bis(trimethylsilyl)amide;
Py	Pyridine;
TFA	Trifluoroacetic acid;
THF	Tetrahydrofuran.

The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic,

maleic, hydroxymaleic, phenyl-acetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The farnesyl transferase inhibitors of formula (II-a) through (II-c) can be synthesized in accordance with reaction schemes 1-16, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^a and R^b, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Reaction Schemes.

<u>Synopsis of reaction Schemes 1-16:</u>

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. In Scheme 1, for example, the synthesis of 2-alkyl substituted piperazines is outlined, and is essentially that described by

J. S. Kiely and S. R. Priebe in Organic Preparations and Proceedings Int., **1990**, *22*, 761-768. Boc-protected amino acids I, available commercially or by procedures known to those skilled in the art, can be coupled to N-benzyl amino acid esters using a variety of dehydrating agents such as DCC (dicyclohexycarbodiimide) or EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) in a solvent such as methylene chloride, chloroform, dichloroethane, or in dimethylformamide. The product II is then deprotected with acid, for example hydrogen chloride in chloroform or ethyl acetate, or trifluoroacetic acid in methylene chloride, and cyclized under weakly basic conditions to give the diketopiperazine III. Reduction of III with lithium aluminum hydride in refluxing ether gives the piperazine IV, which is protected as the Boc derivative V. The N-benzyl group can be cleaved under standard conditions of hydrogenation, e.g., 10% palladium on carbon at 60 psi hydrogen on a Parr apparatus for 24-48 h. The product VI can be treated with an acid chloride, or a carboxylic acid under standard dehydrating conditions to furnish the carboxamides VII. A final acid deprotection step gives the intermediate VIII (Scheme 2). Intermediate VIII can be reductively alkylated with a variety of aldehydes, such as IX, prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid (Scheme 3). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as dichloroethane, methanol or dimethylformamide. The product X can be deprotected to give the final compounds XI with trifluoroacetic acid in methylene chloride. The final product XI is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XI can further be selectively protected to obtain XII, which can subsequently be reductively alkylated with a second aldehyde to obtain XIII. Removal of the protecting group, and conversion to the cyclized product such as the dihydroimidazole XV, can be accomplished by literature procedures.

Alternatively, the protected piperazine intermediate VII can be reductively alkylated with other aldehydes such as 1-trityl-4-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products such as XVI (Scheme IV) (Tr = trityl). The trityl protecting group can be removed from XVI to give XVII, or alternatively, XVI can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole XVIII. Alternatively, the intermediate VIII can be acylated or sulfonylated by standard techniques. The imidazole acetic acid XIX can be converted to the acetate XXI by standard procedures, and XXI can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XXII. Hydrolysis and reaction with piperazine VIII in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XXIV.

If the piperazine VIII is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XXV in Scheme 6, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 6, 7). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXIX. In addition, the fully deprotected amino alcohol XXX can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXXI (Scheme 7), or tertiary amines.

The protected amino alcohol XXVII can also be utilized to synthesize 2-aziridinylmethylpiperazines such as XXXII (Scheme 8). Treating XXVII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide leads to the formation of aziridine XXXII. The aziridine reacts in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXXIII.

Piperazine VIII can be reacted with an aldehyde derived from an amino acid, such as an O-alkylated tyrosine, to obtain compounds such as XXXIX. When R' is an aryl group, XXXIX can first be hydrogenated to unmask the phenol, and the amine group

deprotected with acid to produce XL. Alternatively, the amine protecting group in XXXIX can be removed, and O-alkylated phenolic amines such as XLI produced.

Depending on the identity of the amino acid I, various side chains can be incorporated onto the piperazine. For example, when I is a protected β-benzyl ester of aspartic acid, the intermediate diketopiperazine XLII (where n=1 and R=benzyl) is obtained, as shown in Scheme 10. Subsequent reduction reduces the ester to the alcohol XLIII, which can then be reacted with a variety of alkylating agents such as an alkyl iodide, under basic conditions, for example, sodium hydride in dimethylformamide or tetrahydrofuran. The resulting ether XLIV can then be carried on to final products as described in Schemes 3-9.

N-Aryl piperazines can be prepared as described in Scheme 11. An aryl amine XLV is reacted with *bis* -chloroethyl amine hydrochloride (XLVI) in refluxing *n* -butanol to furnish compounds XLVII. The resulting piperazines XLVII can then be carried on to final products as described in Schemes 3-9.

Piperazin-5-ones can be prepared as shown in Scheme 12. Reductive amination of protected amino aldehydes XLIX (prepared from I as described previously) gives rise to compound L. This is then reacted with bromoacetyl bromide under Schotten-Baumann conditions. Ring closure is effected with a base, such as sodium hydride, in a polar aprotic solvent, such as dimethylformamide, to give LI. The carbamate protecting group is removed under acidic conditions, such as trifluoroacetic acid in methylene chloride or hydrogen chloride gas in methanol or ethyl acetate, and the resulting piperazine can then be carried on to final products as described in Schemes 3-9.

The isomeric piperazin-3-ones can be prepared as described in Scheme 13. The imine formed from arylcarboxamides LII and 2-aminoglycinal diethyl acetal (LIII) can be reduced under a variety of conditions, including sodium triacetoxyborohydride in dichloroethane, to give the amine LIV. Amino acids I can be coupled to amines LIV under standard conditions, and the resulting amide LV when treated

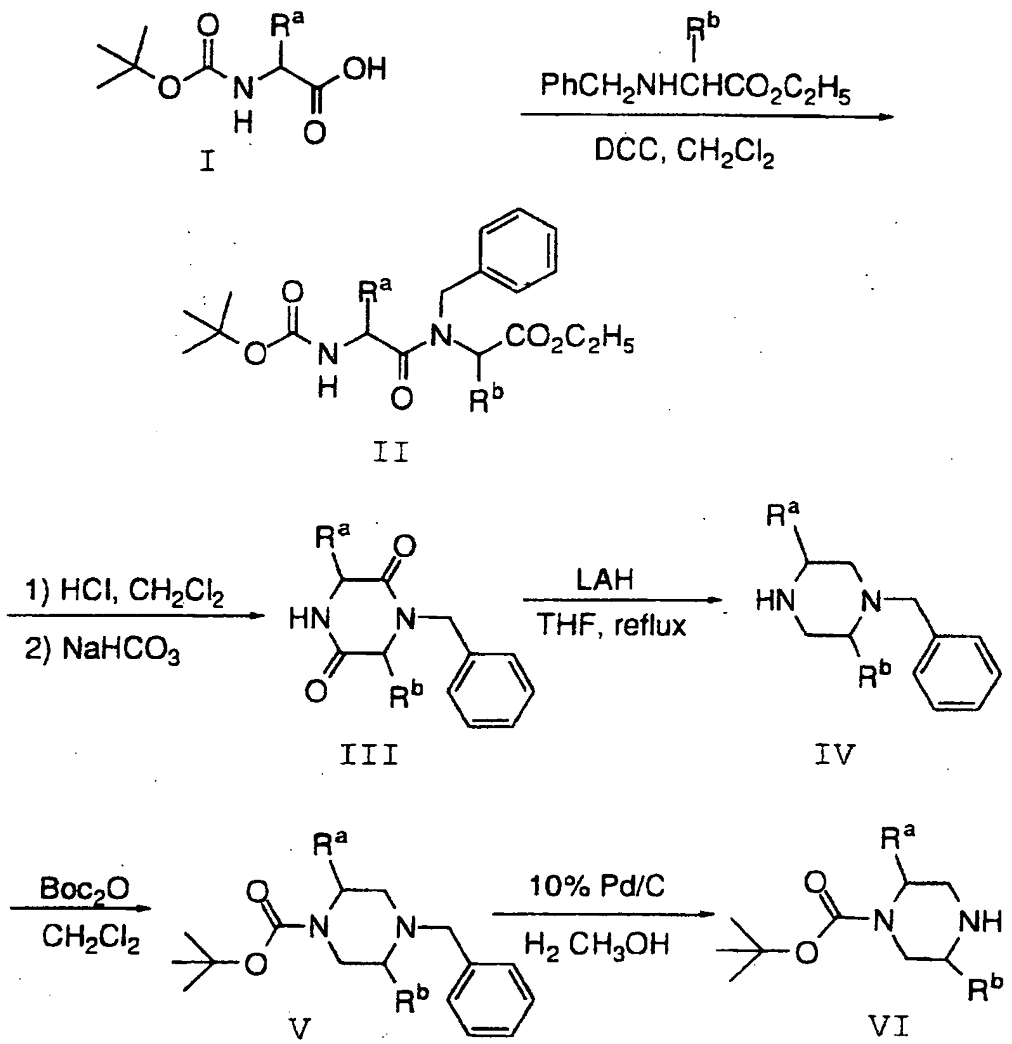
with aqueous acid in tetrahydrofuran can cyclize to the unsaturated LVI. Catalytic hydrogenation under standard conditions gives the requisite intermediate LVII, which is elaborated to final products as described in Schemes 3-9.

Access to alternatively substituted piperazines is described in Scheme 14. Following deprotection, e.g., with trifluoroacetic acid, the N-benzyl piperazine V can be acylated with an aryl carboxylic acid. The resulting N-benzyl aryl carboxamide LIX can be hydrogenated in the presence of a catalyst to give the piperazine carboxamide LX which can then be carried on to final products as described in Schemes 3-9.

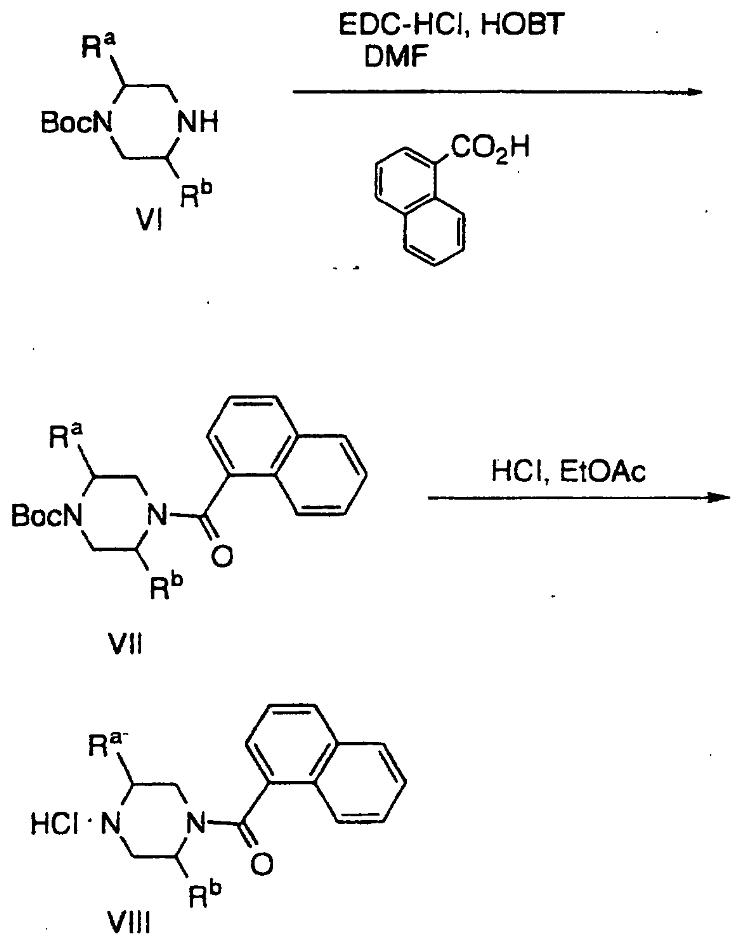
Reaction Scheme 15 provides an example of the synthesis of compounds wherein the substituents R^2 and R^3 are combined to form - $(CH_2)_u$ -. For example, 1-aminocyclohexane-1-carboxylic acid LXI can be converted to the spiropiperazine LXVI essentially according to the procedures outlined in Schemes 1 and 2. The piperazine intermediate LXIX can be deprotected as before, and carried on to final products as described in Schemes 3-9. It is understood that reagents utilized to provide the substituent Y which is 2-(naphthyl) and the imidazolylalkyl substituent may be readily replaced by other reagents well known in the art and readily available to provide other N-substituents on the piperazine.

The aldehyde XLIX from Scheme 12 can also be reductively alkylated with an aniline as shown in Scheme 16. The product LXXI can be converted to a piperazinone by acylation with chloroacetyl chloride to give LXXII, followed by base-induced cyclization to LXXIII. Deprotection, followed by reductive alkylation with a protected imidazole carboxaldehyde leads to LXXV, which can be alkylation with an arylmethylhalide to give the imidazolium salt LXXVI. Final removal of protecting groups by either solvolysis with a lower alkyl alcohol, such as methanol, or treatment with triethylsilane in methylene chloride in the presence of trifluoroacetic acid gives the final product LXXVII.

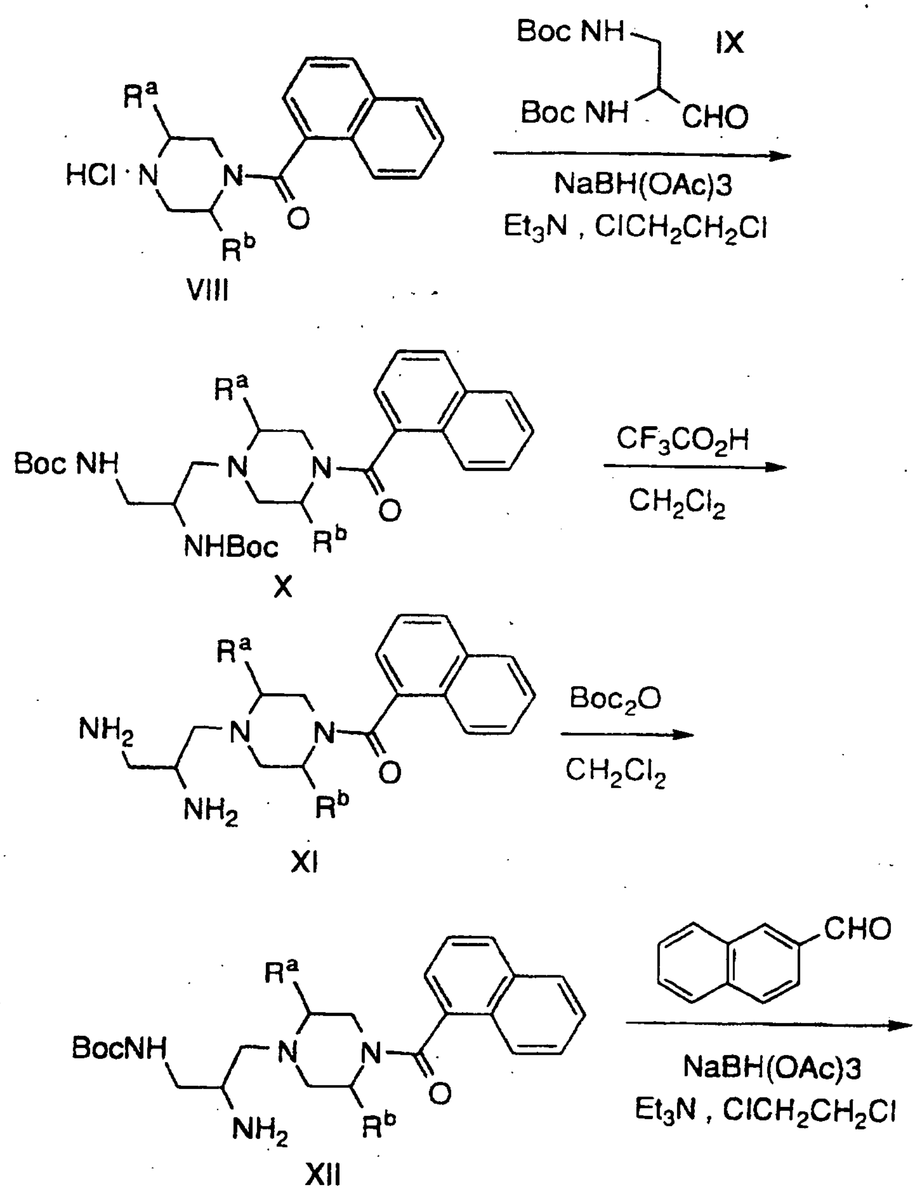
SCHEME 1


PhCH2NHCHCO2C2H5
DCC, CH2Cl2
I
II
1) HCl, CH2Cl2
2) NaHCO3
III
LAH
THF, reflux
IV
Boc2O
CH2Cl2
V
10% Pd/C
H2 CH3OH
VI

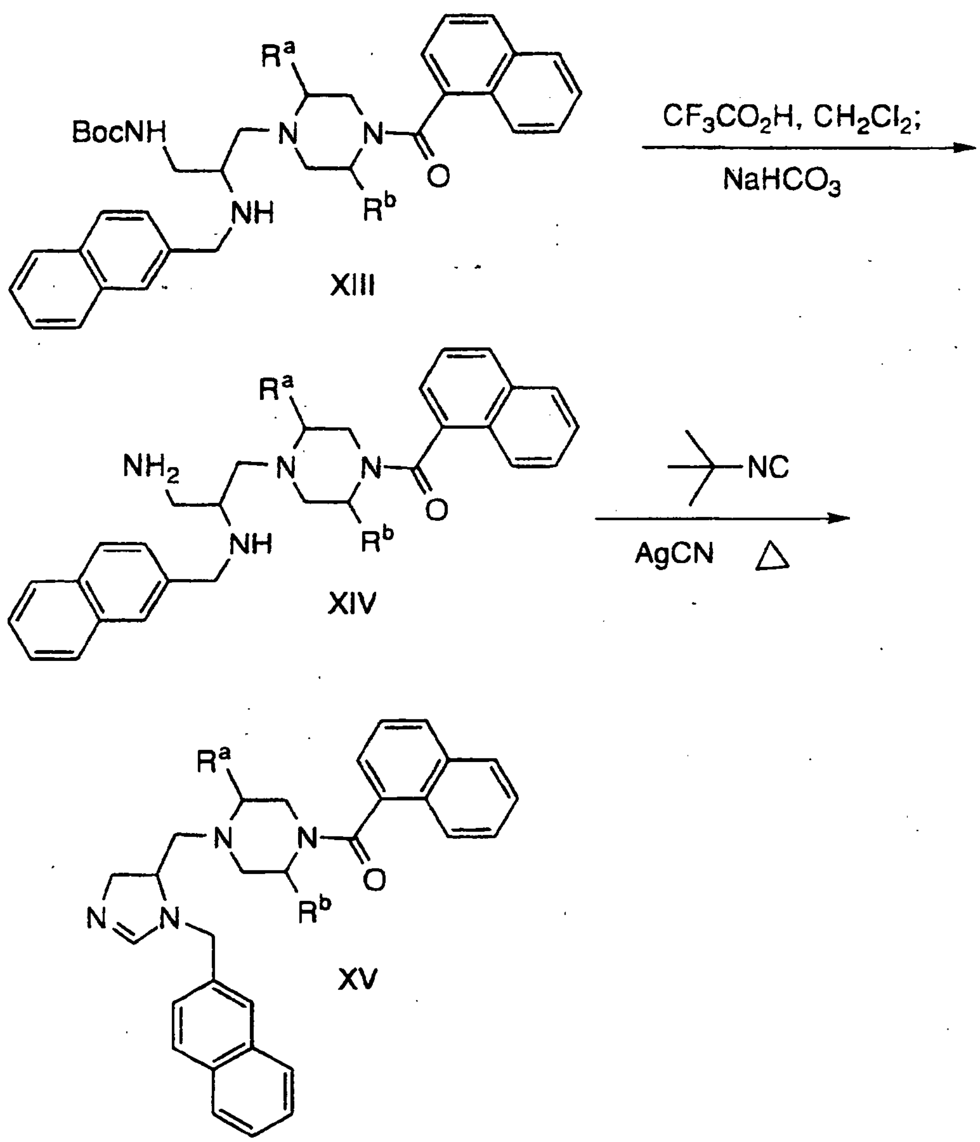
SCHEME 2


EDC-HCl, HOBT
DMF
CO_2H
R^a
BocN
NH
R^b
VI
N
O
VII
HCl, EtOAc
HCl · N
VIII

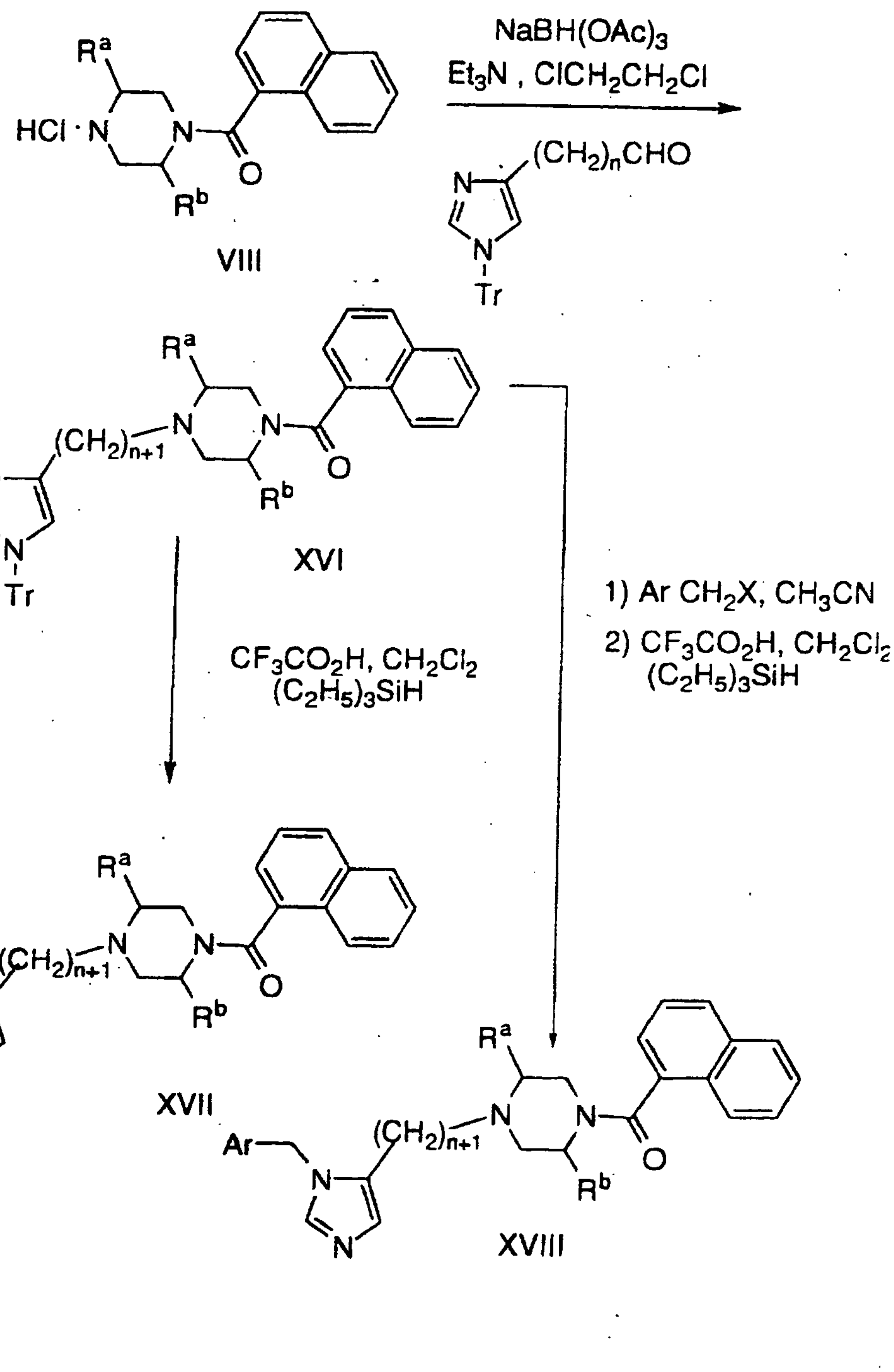
SCHEME 3


Boc NH
IX
Boc NH
CHO
R^a
HCl · N
N
O
R^b
VIII
NaBH(OAc)3
Et3N , ClCH2CH2Cl
Boc NH
NHBoc
X
CF3CO2H
CH2Cl2
NH2
NH2
XI
Boc2O
CH2Cl2
BocNH
NH2
XII
CHO
NaBH(OAc)3
Et3N , ClCH2CH2Cl

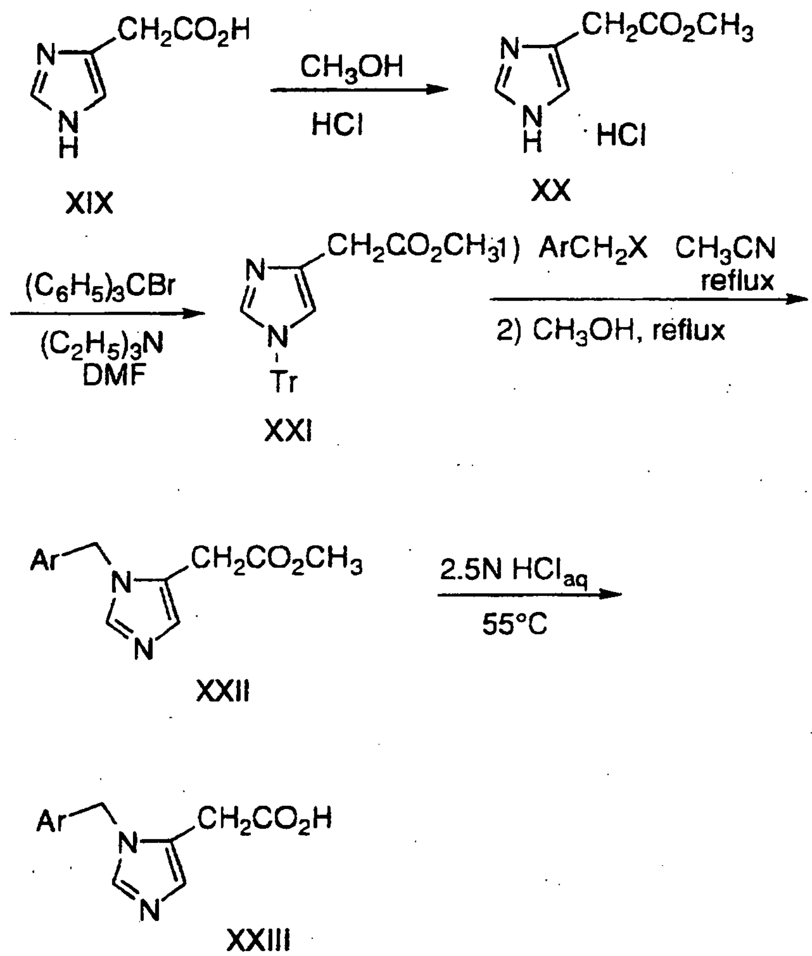
SCHEME 3 (Cont.)



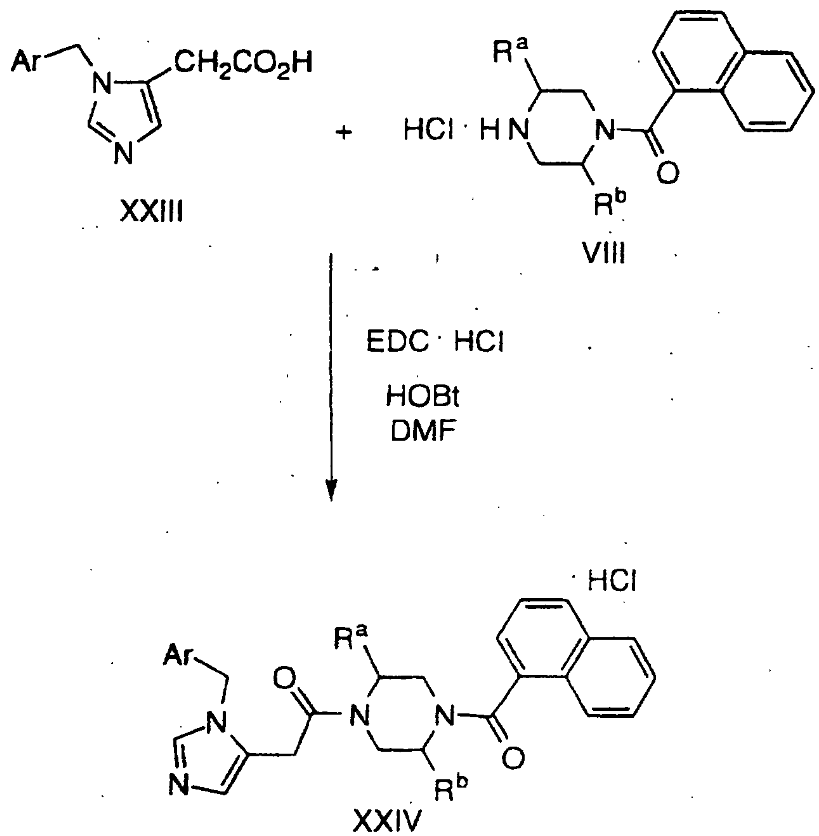
SCHEME 4


NaBH(OAc)3
Et3N , ClCH2CH2Cl
(CH2)nCHO
N
N
Tr
Ra
HCl · N
N
O
Rb
VIII
(CH2)n+1
XVI
CF3CO2H, CH2Cl2
(C2H5)3SiH
1) Ar CH2X, CH3CN
2) CF3CO2H, CH2Cl2
(C2H5)3SiH
XVII
Ar
XVIII

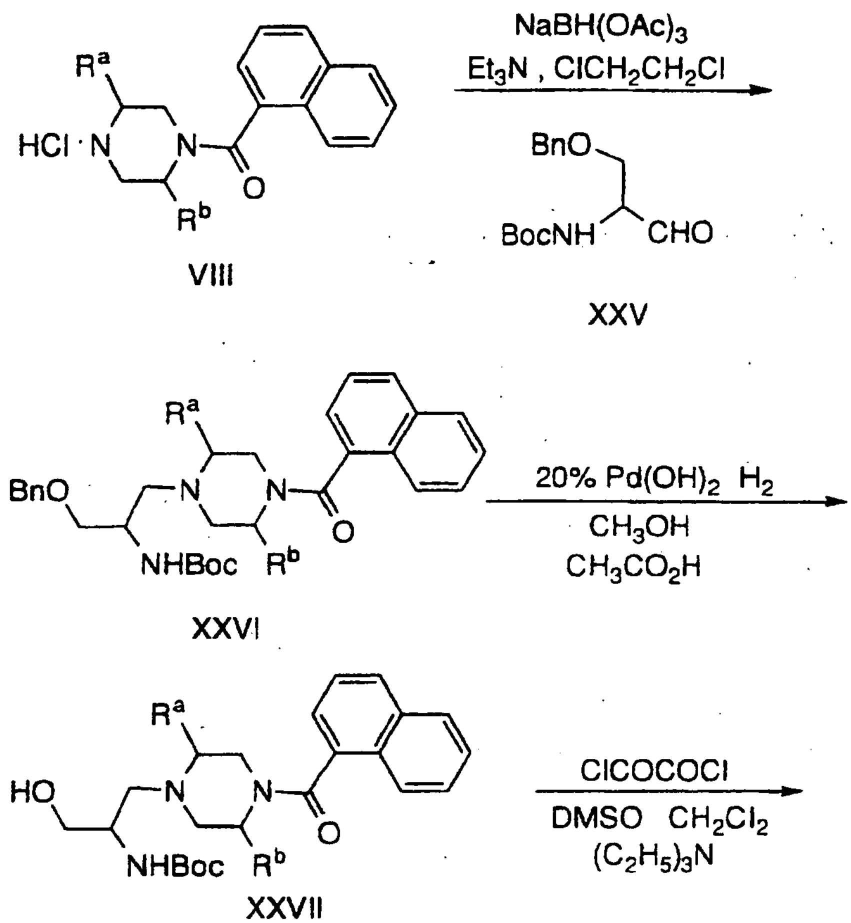
SCHEME 5


CH2CO2H
CH3OH
HCl
CH2CO2CH3
· HCl
XIX
XX
(C6H5)3CBr
(C2H5)3N
DMF
CH2CO2CH3
1) ArCH2X CH3CN reflux
2) CH3OH, reflux
XXI
CH2CO2CH3
2.5N HClaq
55°C
XXII
CH2CO2H
XXIII

SCHEME 5 (continued)

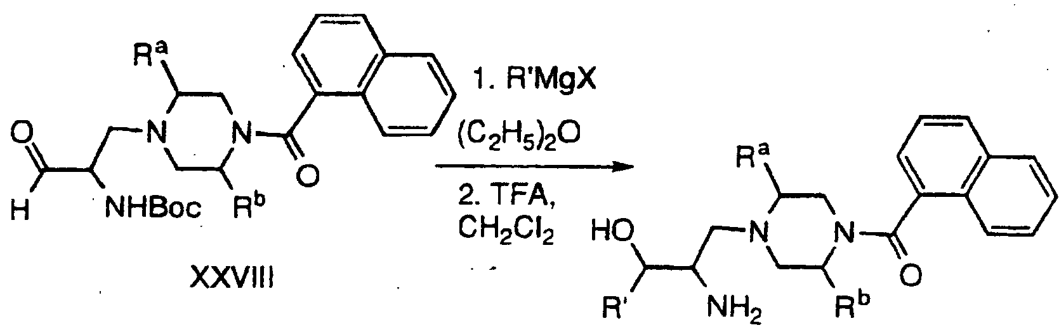


SCHEME 6



NaBH(OAc)3
Et3N , ClCH2CH2Cl
BnO
BocNH
CHO
R^a
HCl · N
N
O
R^b
VIII
XXV
BnO
NHBoc
XXVI
20% Pd(OH)2 H2
CH3OH
CH3CO2H
HO
XXVII
ClCOCOCl
DMSO CH2Cl2
(C2H5)3N

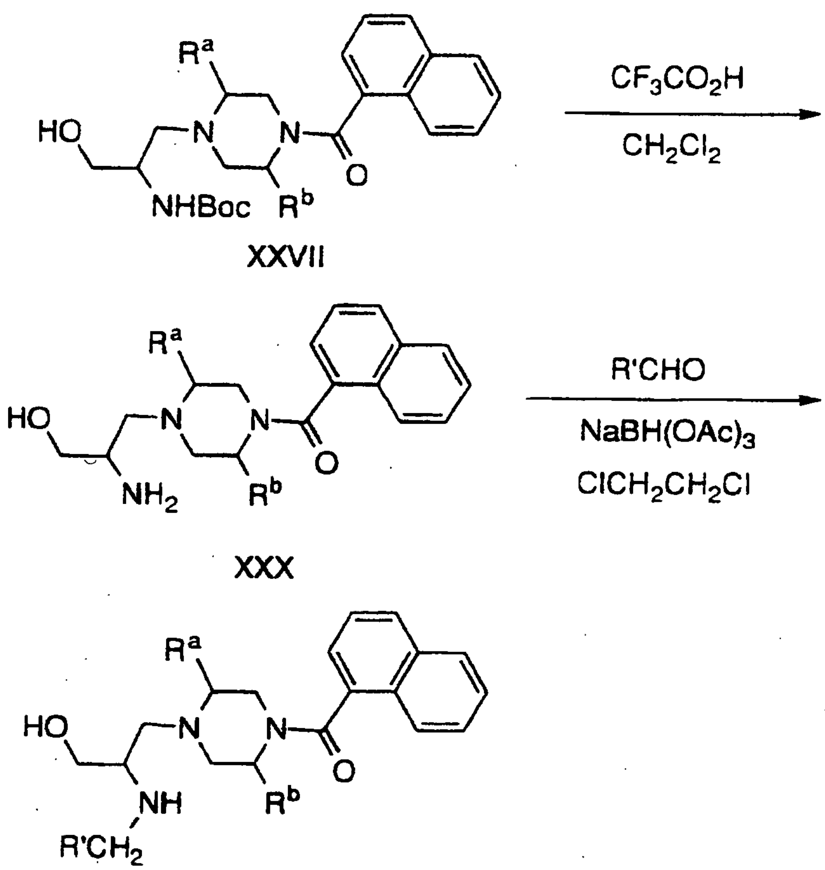
SCHEME 6 (CONTINUED)



XXVIII

XXIX

SCHEME 7

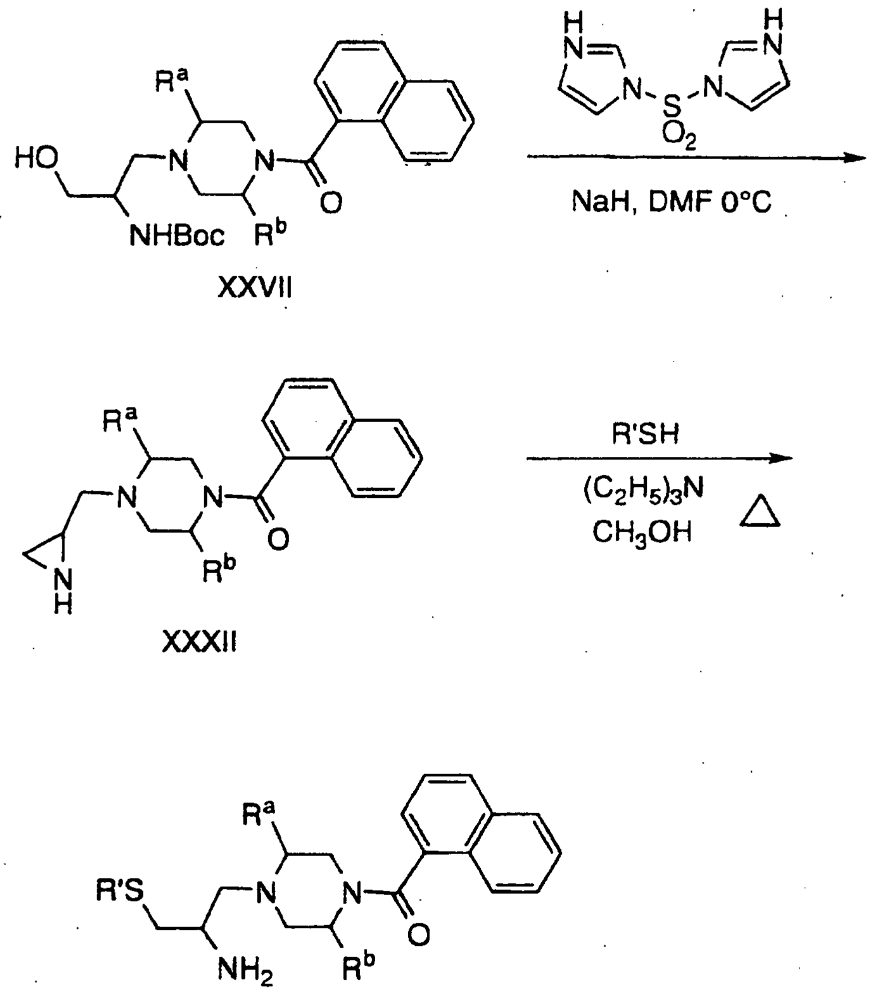


XXVII

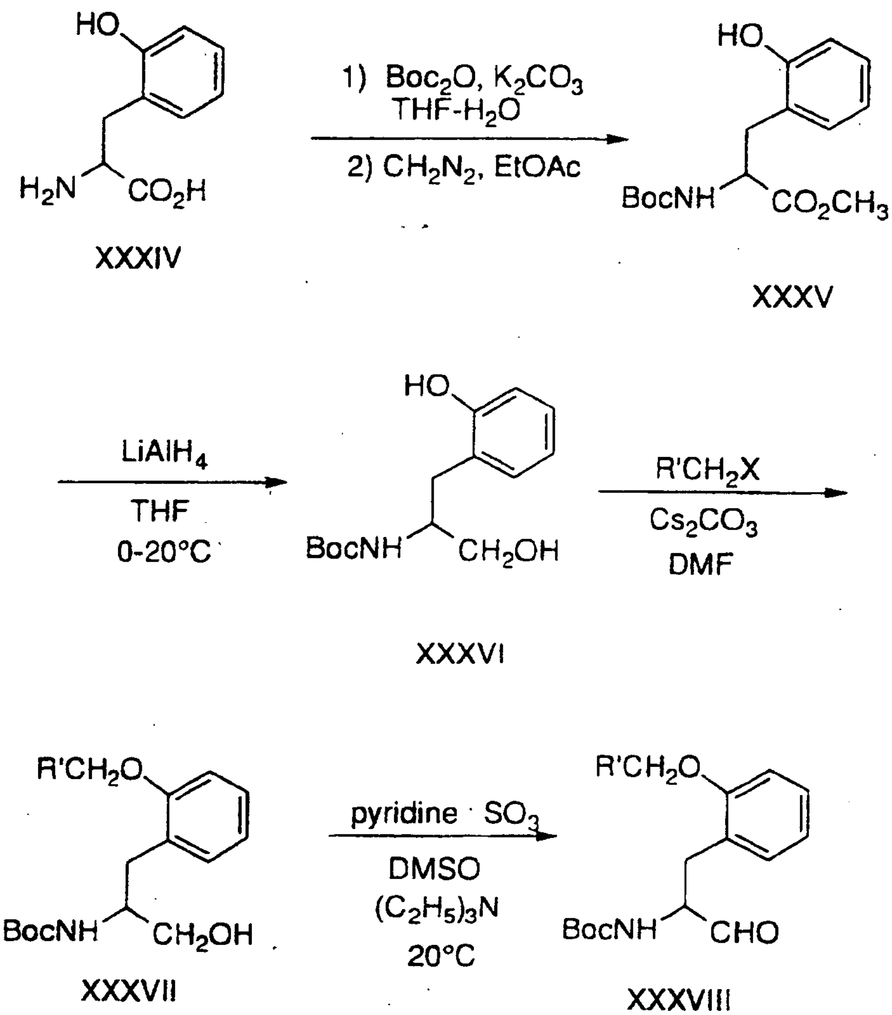
XXX

XXXI

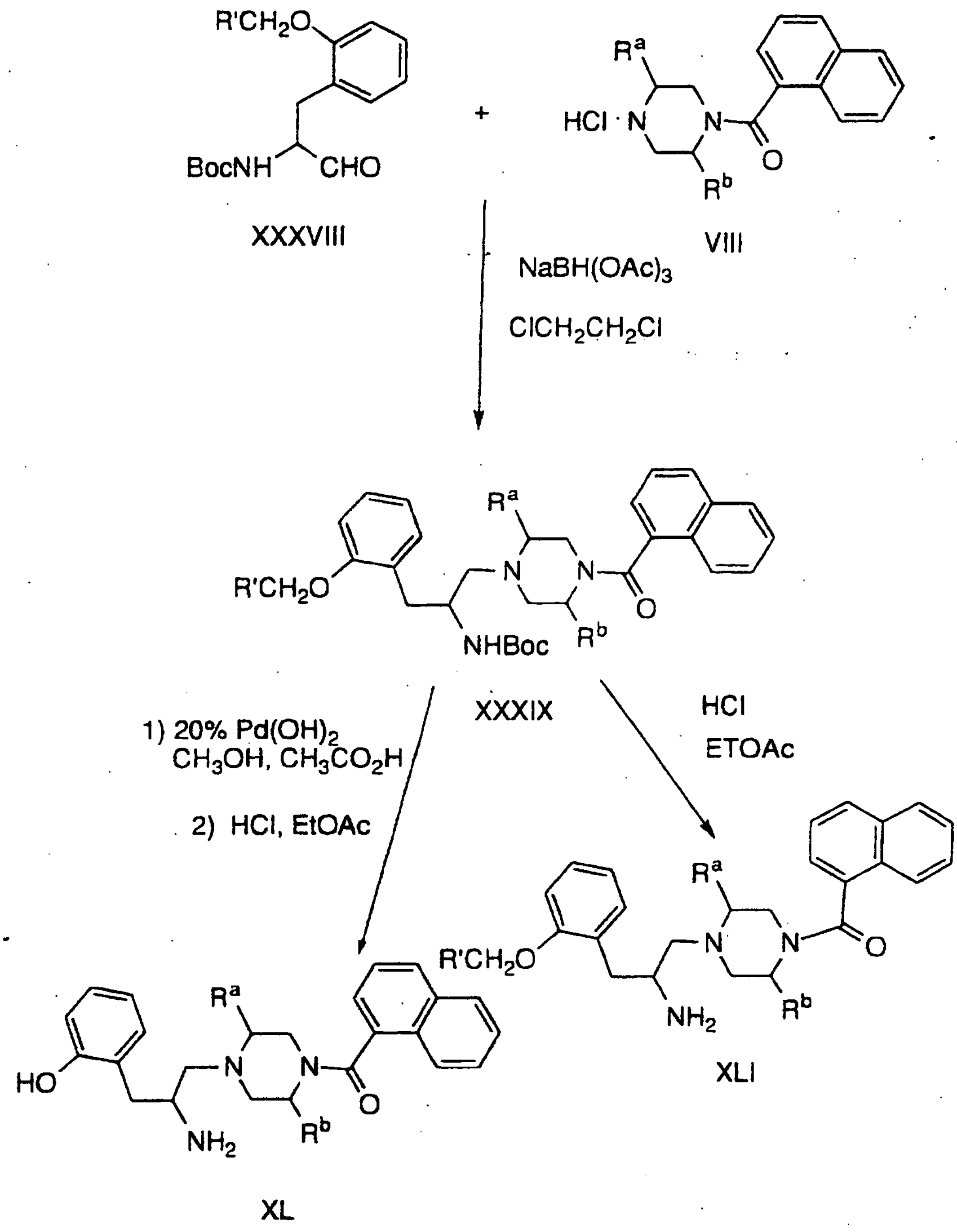
SCHEME 8



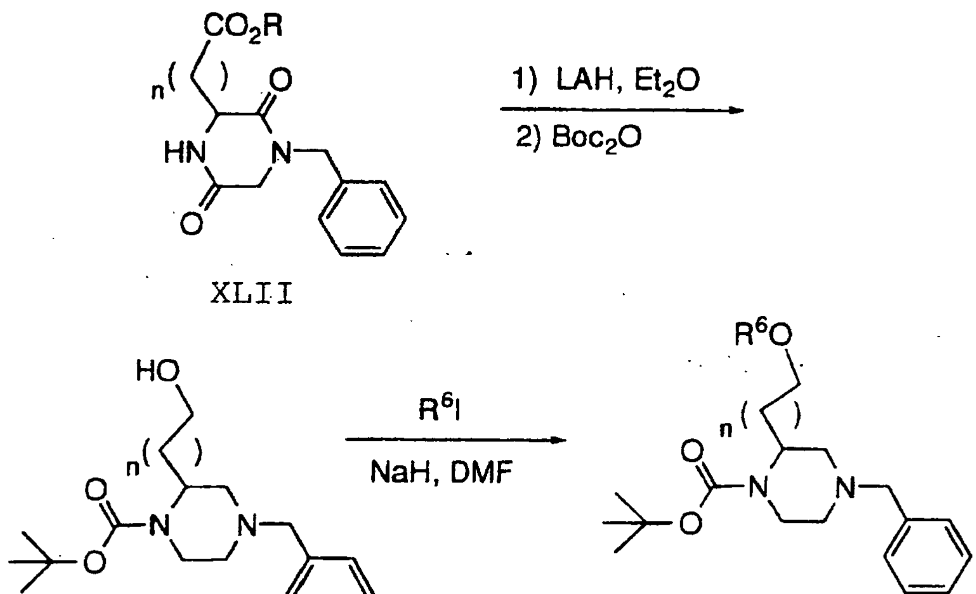
SCHEME 9


XXXIV
1) Boc_2O, K_2CO_3
$THF-H_2O$
2) CH_2N_2, EtOAc
XXXV
$LiAlH_4$
THF
0-20°C
XXXVI
$R'CH_2X$
Cs_2CO_3
DMF
XXXVII
pyridine · SO_3
DMSO
$(C_2H_5)_3N$
20°C
XXXVIII

SCHEME 9 (continued)



SCHEME 10

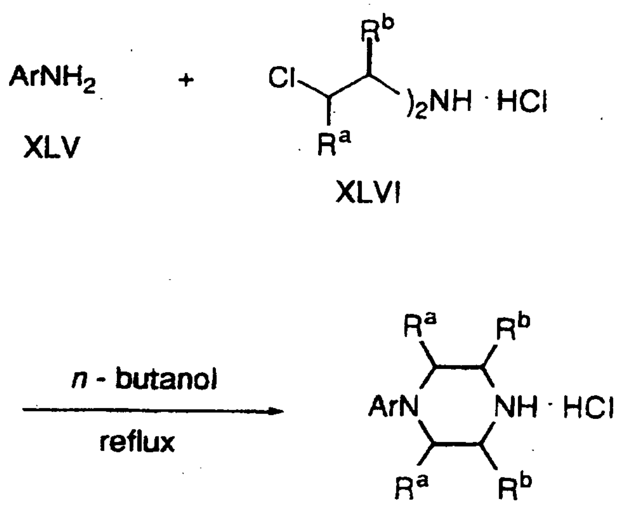


XLII

XLIII

XLIV

SCHEME 11

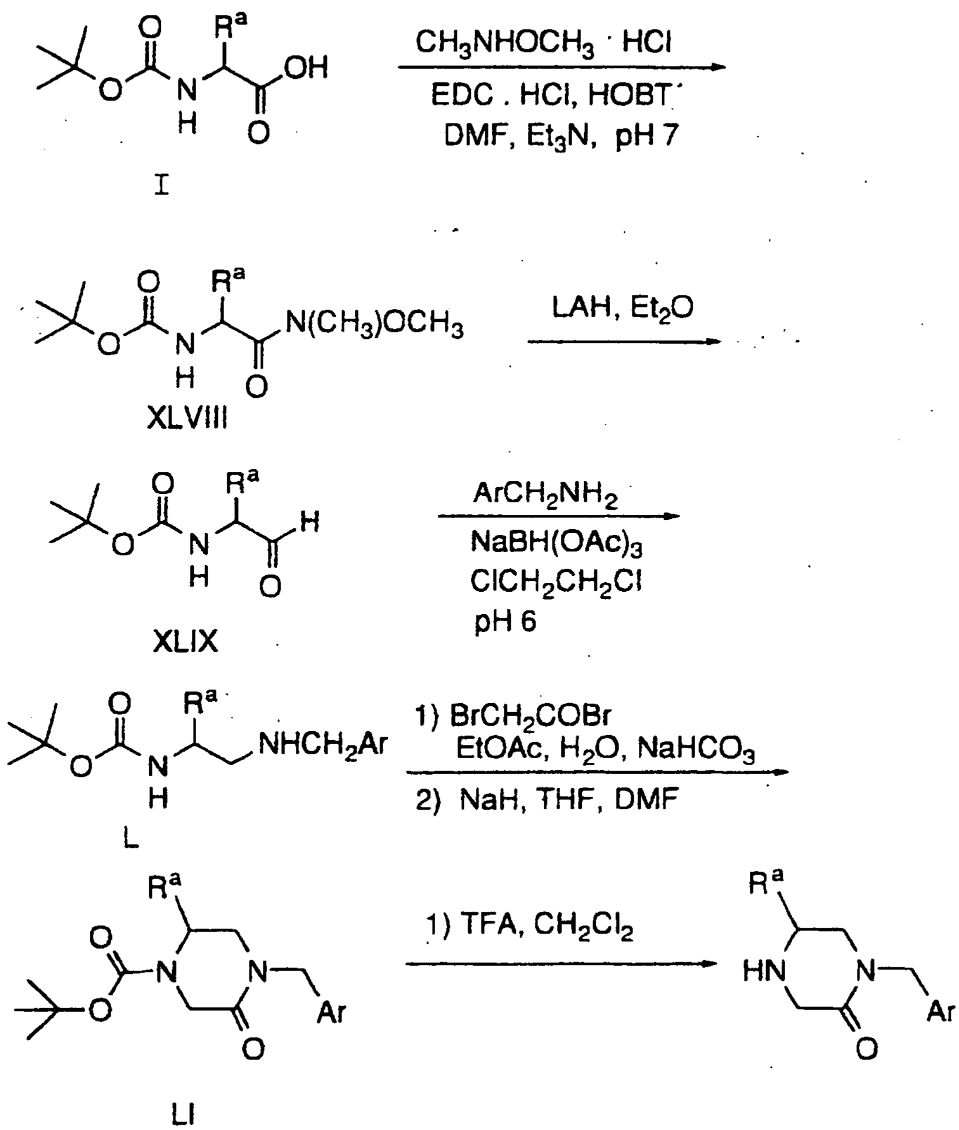


XLV

XLVI

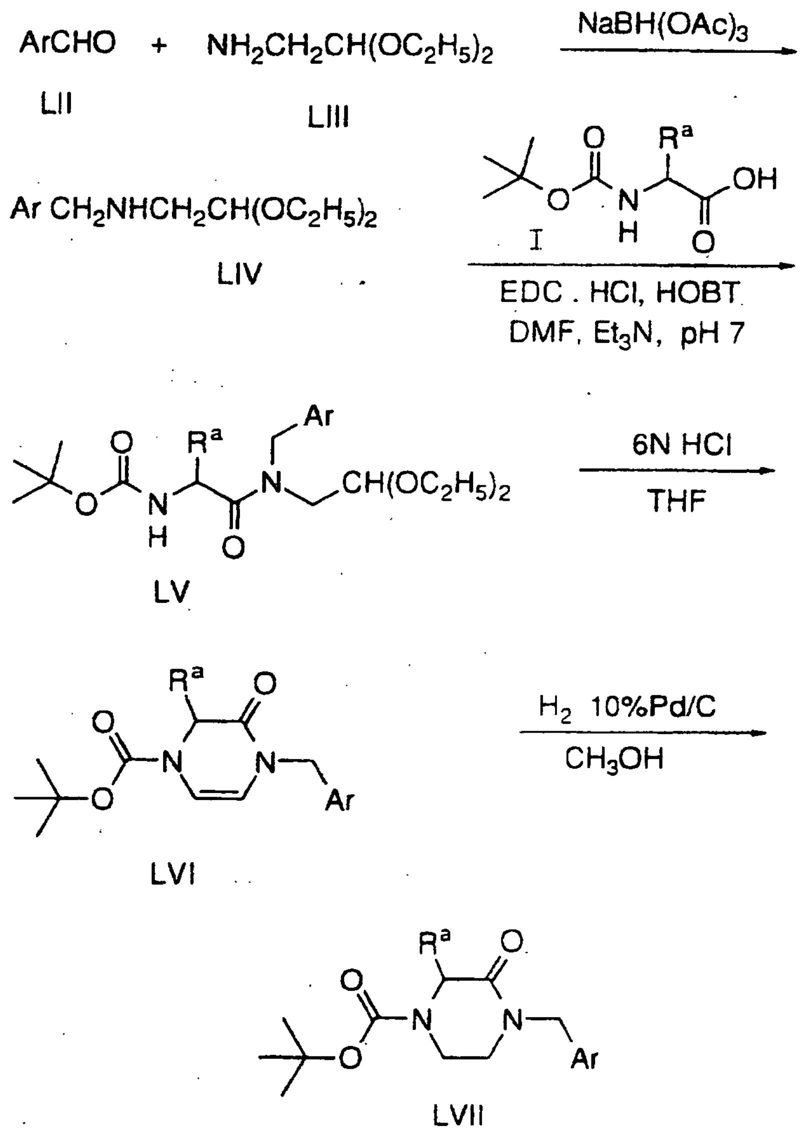
XLVII

SCHEME 12

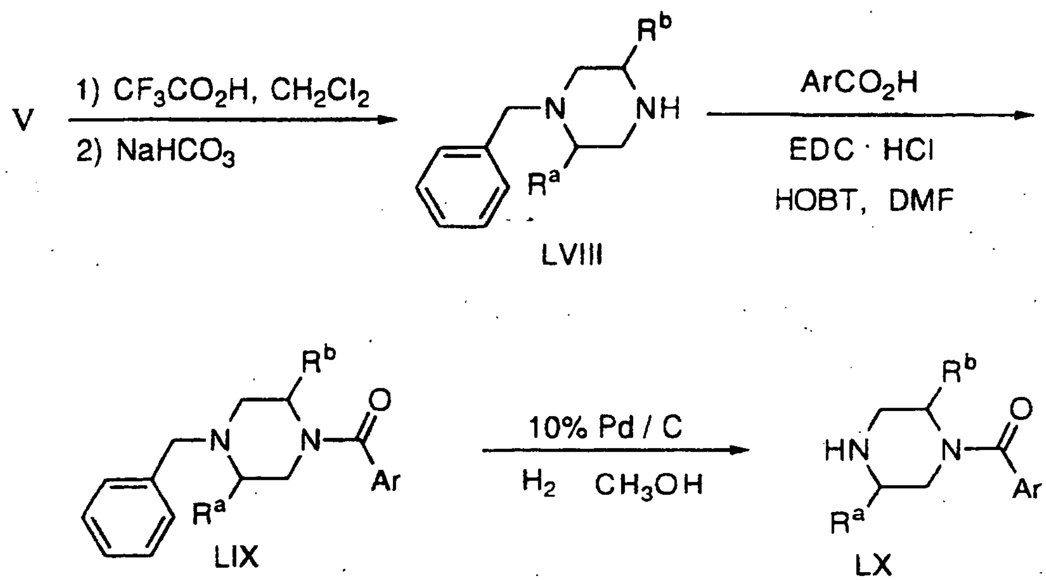


I
$CH_3NHOCH_3 \cdot HCl$
EDC . HCl, HOBT
DMF, Et_3N, pH 7
XLVIII
LAH, Et_2O
XLIX
$ArCH_2NH_2$
$NaBH(OAc)_3$
$ClCH_2CH_2Cl$
pH 6
L
1) $BrCH_2COBr$
EtOAc, H_2O, $NaHCO_3$
2) NaH, THF, DMF
LI
1) TFA, CH_2Cl_2

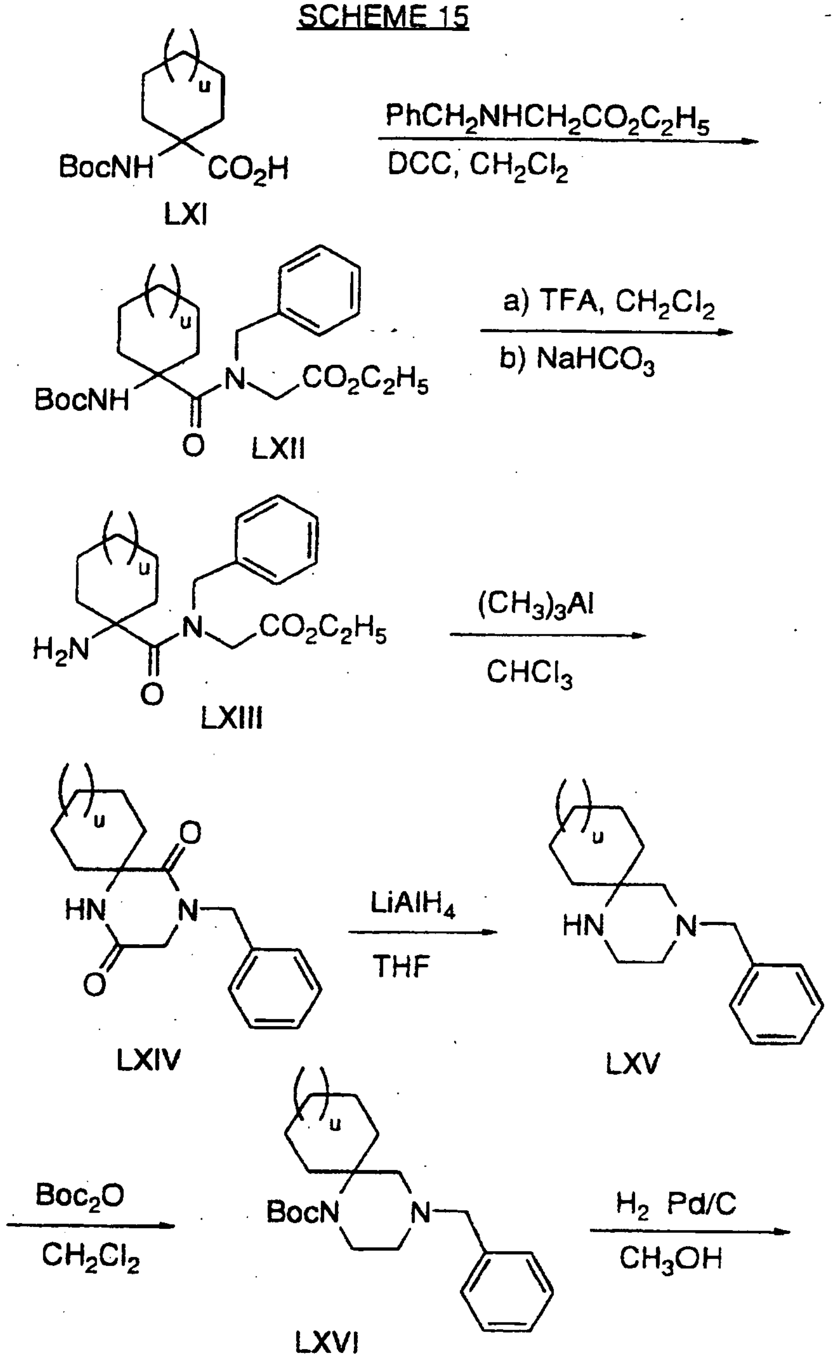
SCHEME 13


ArCHO
+
NH2CH2CH(OC2H5)2
NaBH(OAc)3
LII
LIII
Ar CH2NHCH2CH(OC2H5)2
LIV
I
EDC . HCl, HOBT
DMF, Et3N, pH 7
CH(OC2H5)2
6N HCl
THF
LV
H2 10%Pd/C
CH3OH
LVI
LVII

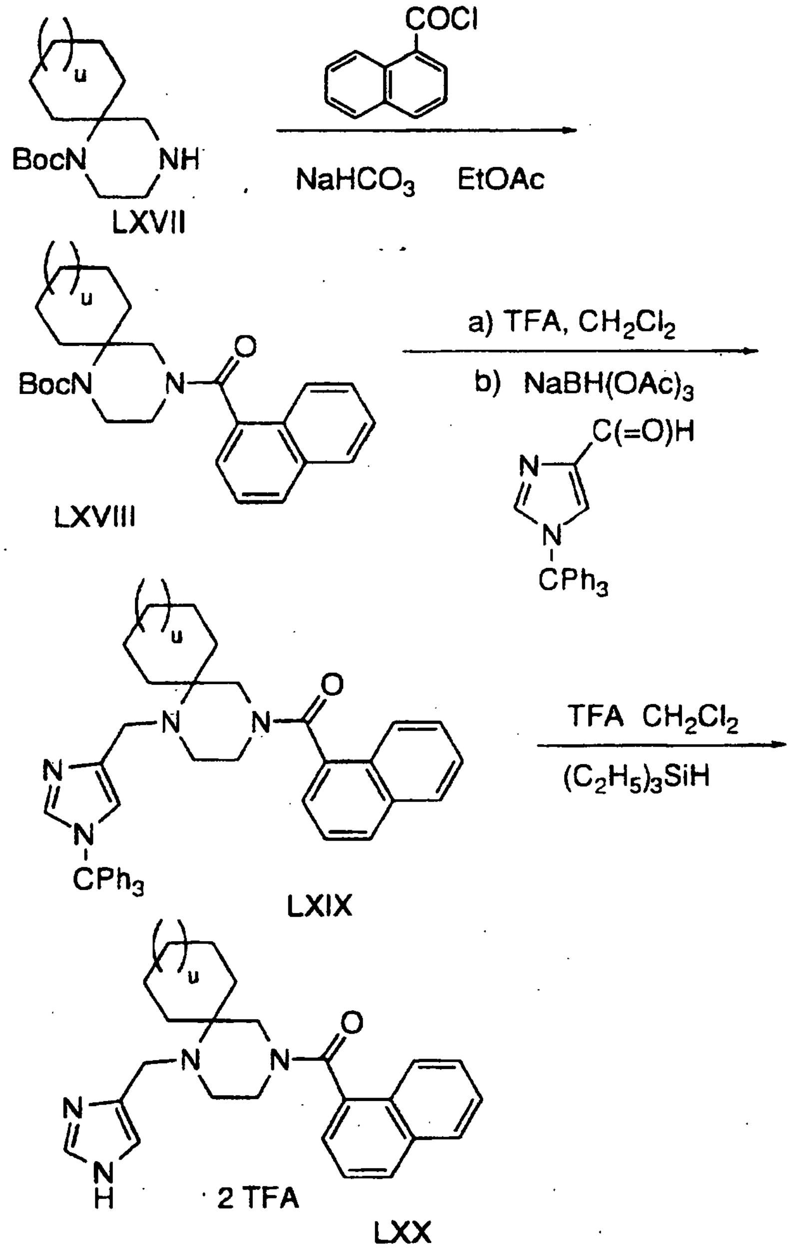
SCHEME 14


V
1) CF_3CO_2H, CH_2Cl_2
2) $NaHCO_3$
LVIII
$ArCO_2H$
EDC · HCl
HOBT, DMF
LIX
10% Pd / C
H_2 CH_3OH
LX

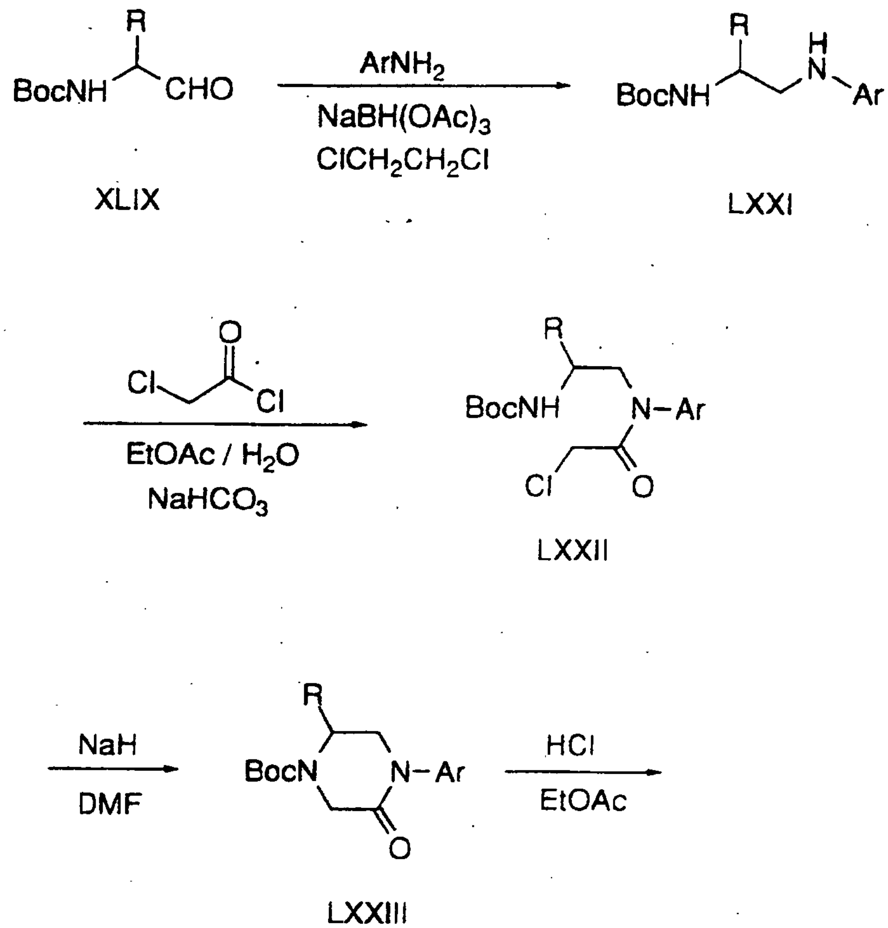
SCHEME 15


BocNH
CO2H
LXI
PhCH2NHCH2CO2C2H5
DCC, CH2Cl2
BocNH
N
CO2C2H5
O
LXII
a) TFA, CH2Cl2
b) NaHCO3
H2N
N
CO2C2H5
O
LXIII
(CH3)3Al
CHCl3
O
HN
N
O
LXIV
LiAlH4
THF
HN
N
LXV
Boc2O
CH2Cl2
BocN
N
LXVI
H2 Pd/C
CH3OH

SCHEME 15 (continued)



SCHEME 16


R
BocNH
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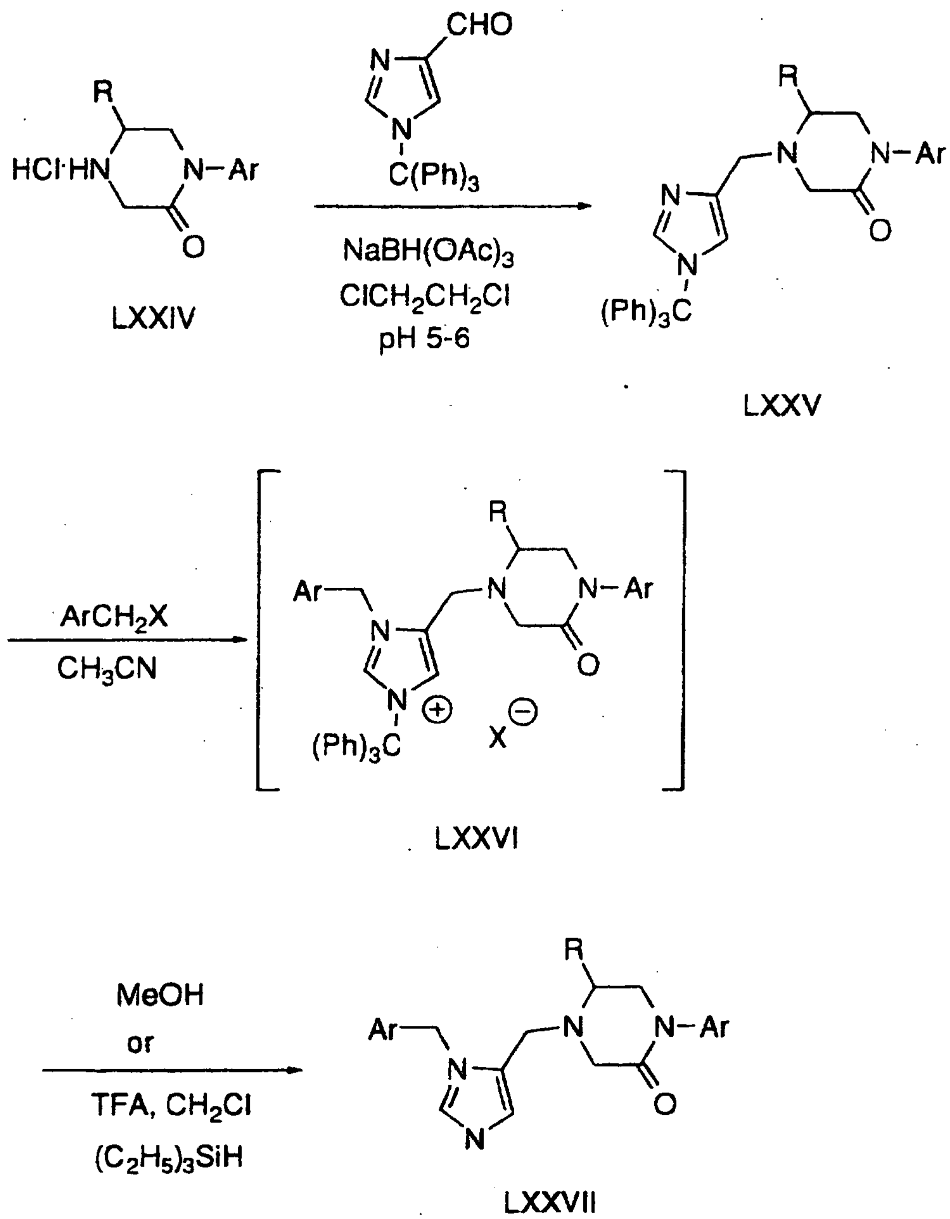
NaBH(OAc)3
ClCH2CH2Cl
XLIX
R
H
N
BocNH
Ar
LXXI
O
Cl
Cl
EtOAc / H2O
NaHCO3
R
BocNH
N-Ar
Cl
O
LXXII
NaH
DMF
R
BocN
N-Ar
O
LXXIII
HCl
EtOAc

SCHEME 16 (continued)



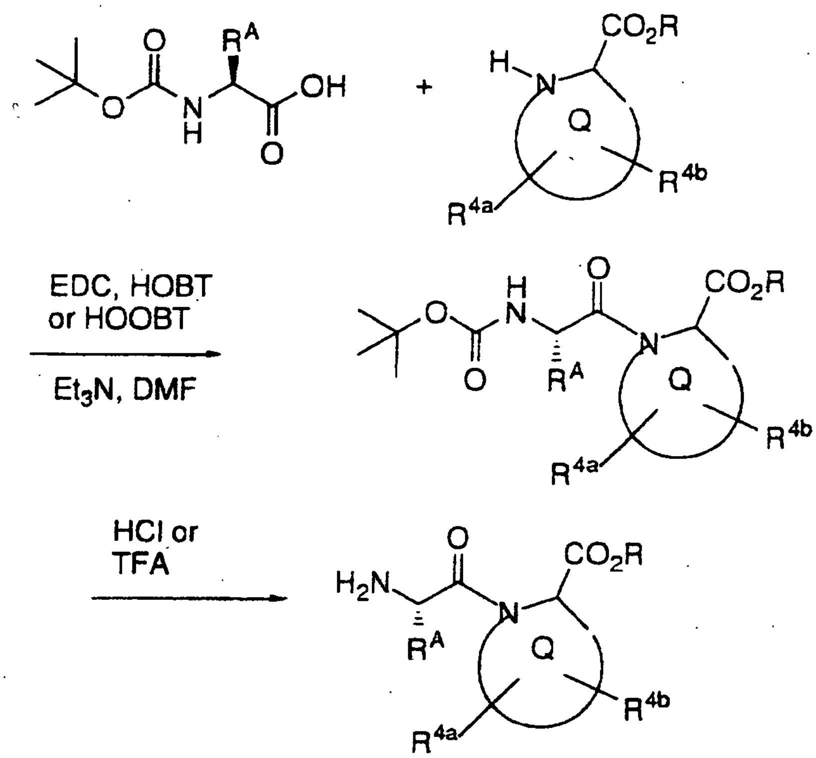
The farnesyl transferase inhibitors can also be synthesized in accordance with the general reaction schemes in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., in accordance with WO 96/10035 published on

April 4, 1996, incorporated herein by reference. In addition to the disclosure contained therein, some alternative reactions are set forth below.

ALTERNATIVE REACTION SCHEME A FOR

COMPOUNDS (II-h) THROUGH (II-o)

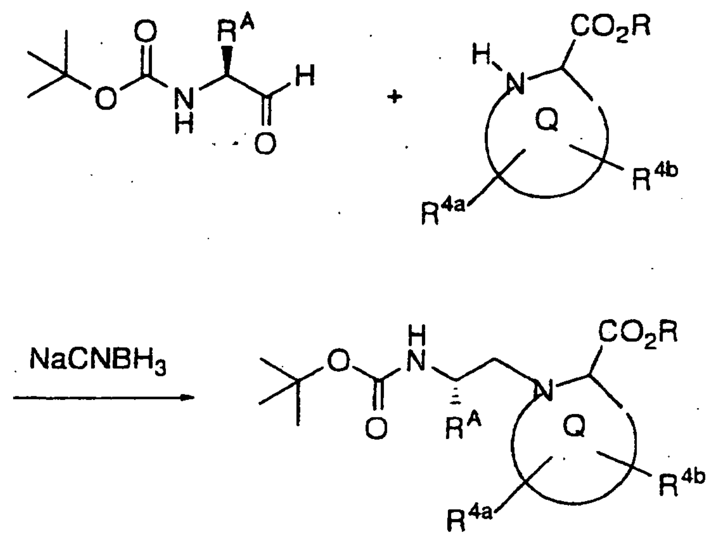
Coupling of residues to form an amide bond



ALTERNATIVE REACTION SCHEME B FOR COMPOUNDS

(II-h) THROUGH (II-o)

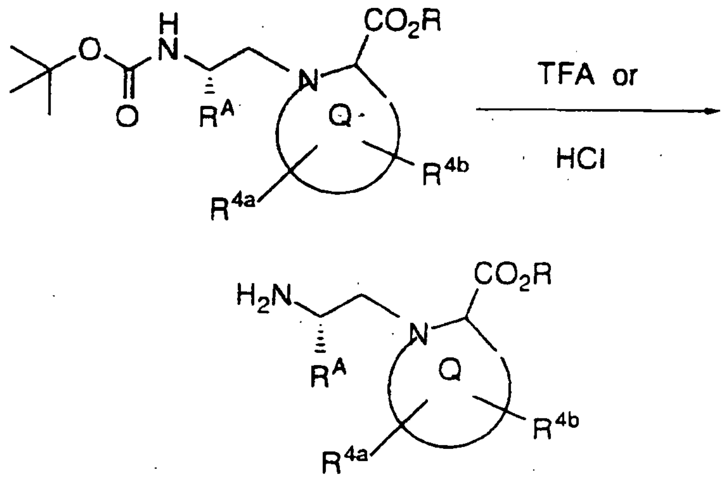
Preparation of reduced peptide subunits by reductive alkylation



ALTERNATIVE REACTION SCHEME C for COMPOUNDS

(II-h) THROUGH (II-o)

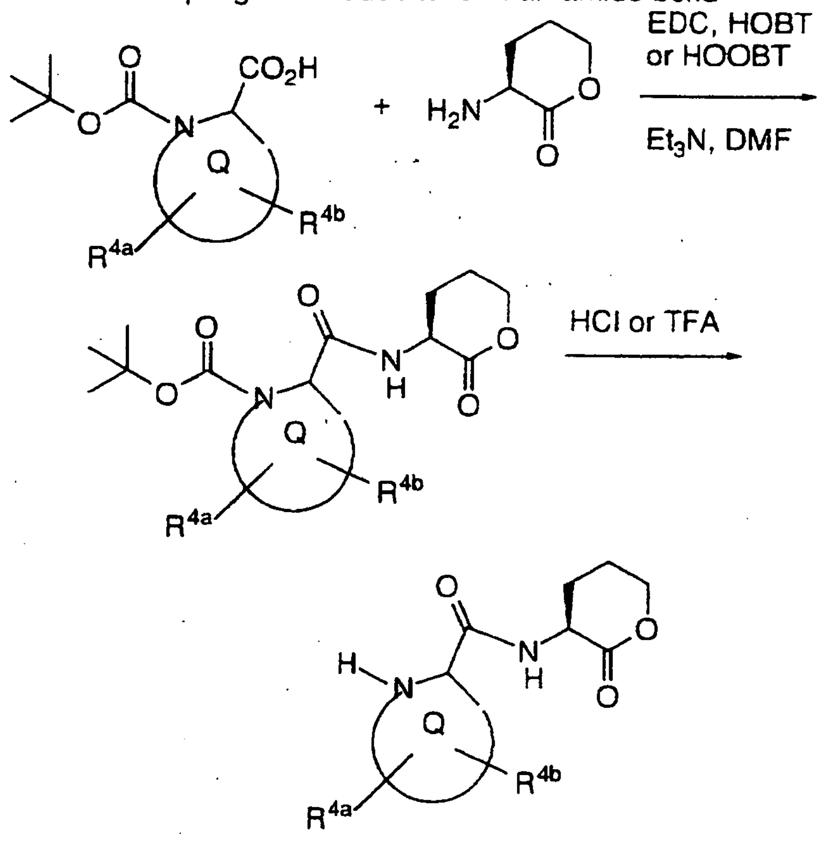
Deprotection of reduced peptide subunits



ALTERNATIVE REACTION SCHEME D FOR COMPOUNDS

(II-h) THROUGH (II-o)

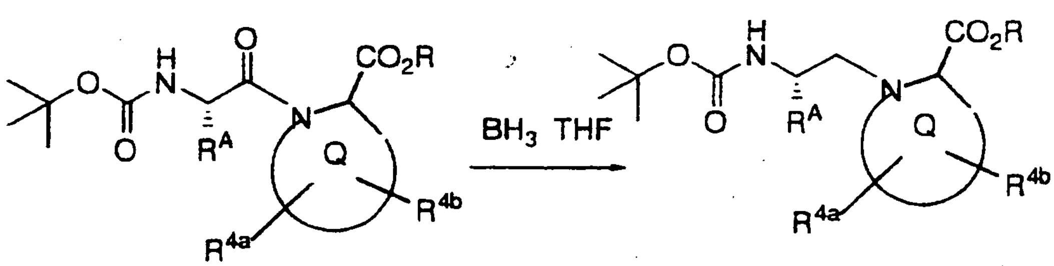
Coupling of residues to form an amide bond



ALTERNATIVE REACTION SCHEME E FOR COMPOUNDS

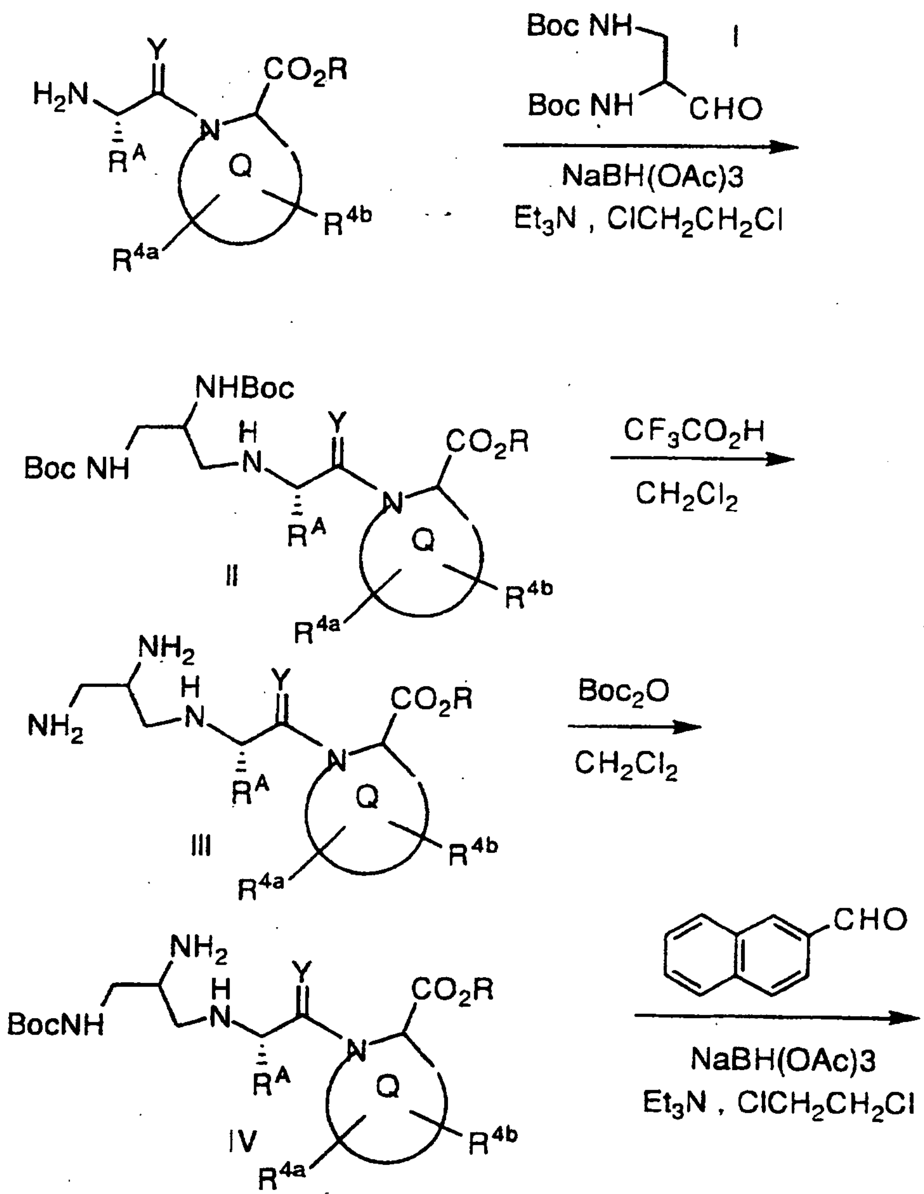
(II-h) THROUGH (II-o)

Preparation of reduced dipeptides from peptides

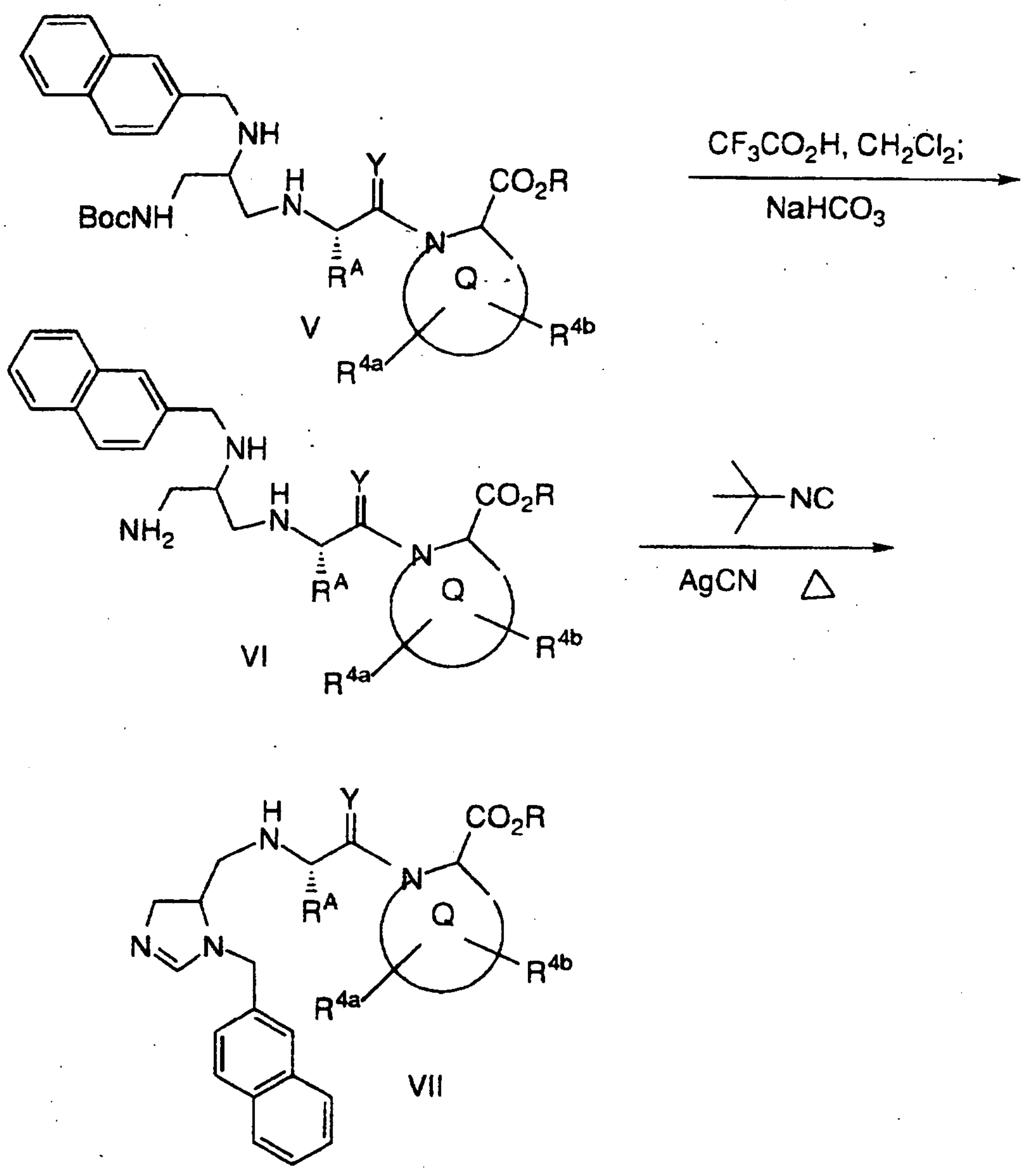


ALTERNATE REACTION SCHEME F FOR

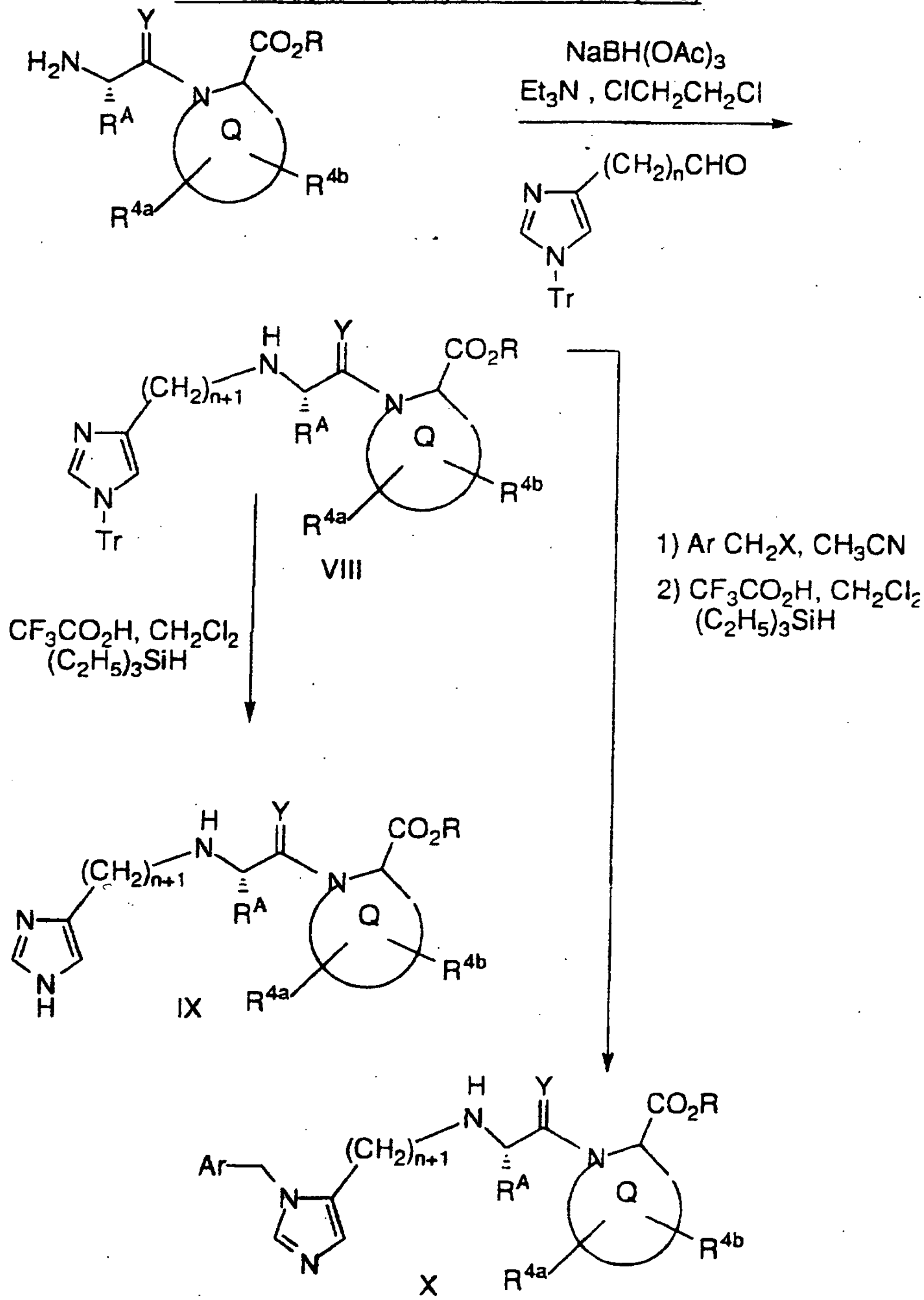
COMPOUNDS (II-h) THROUGH (II-o)



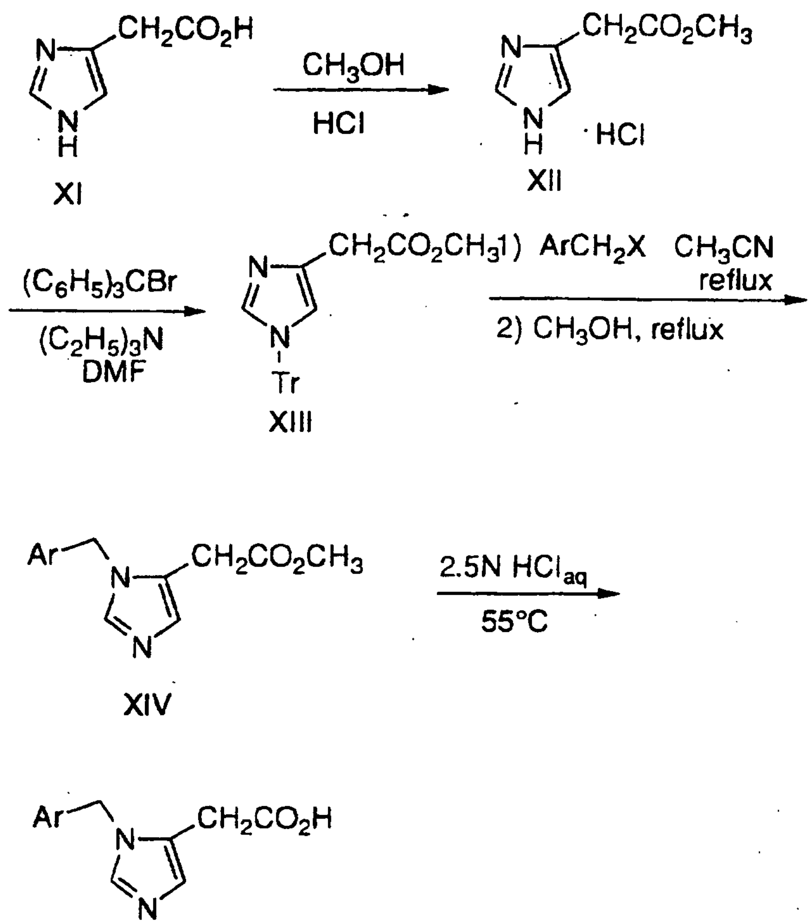
ALTERNATE REACTION SCHEME F (continued)



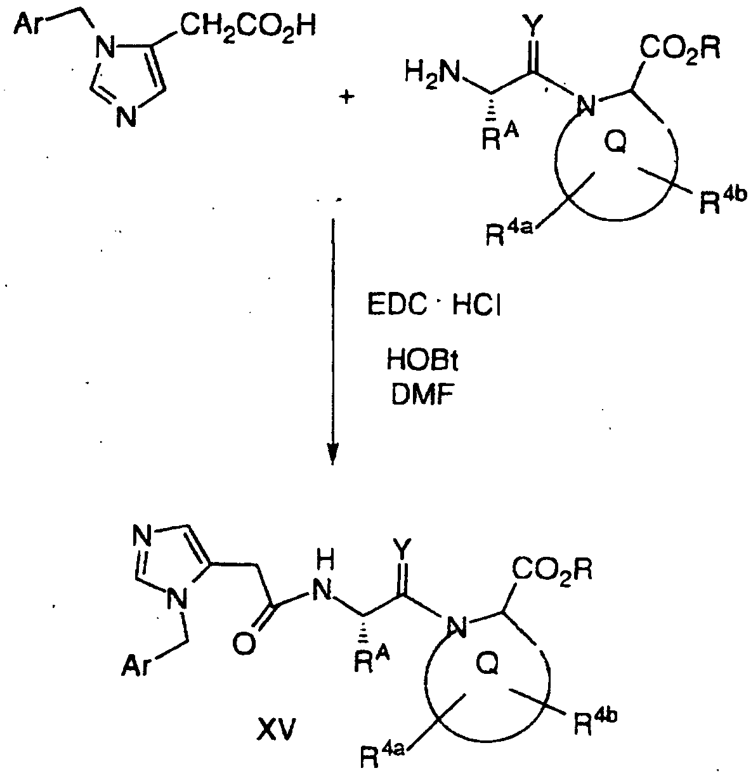
ALTERNATE REACTION SCHEME G FOR COMPOUNDS (II-h) THROUGH (II-o)



ALTERNATE REACTION SCHEME H FOR COMPOUNDS (II-h) THROUGH (II-o)

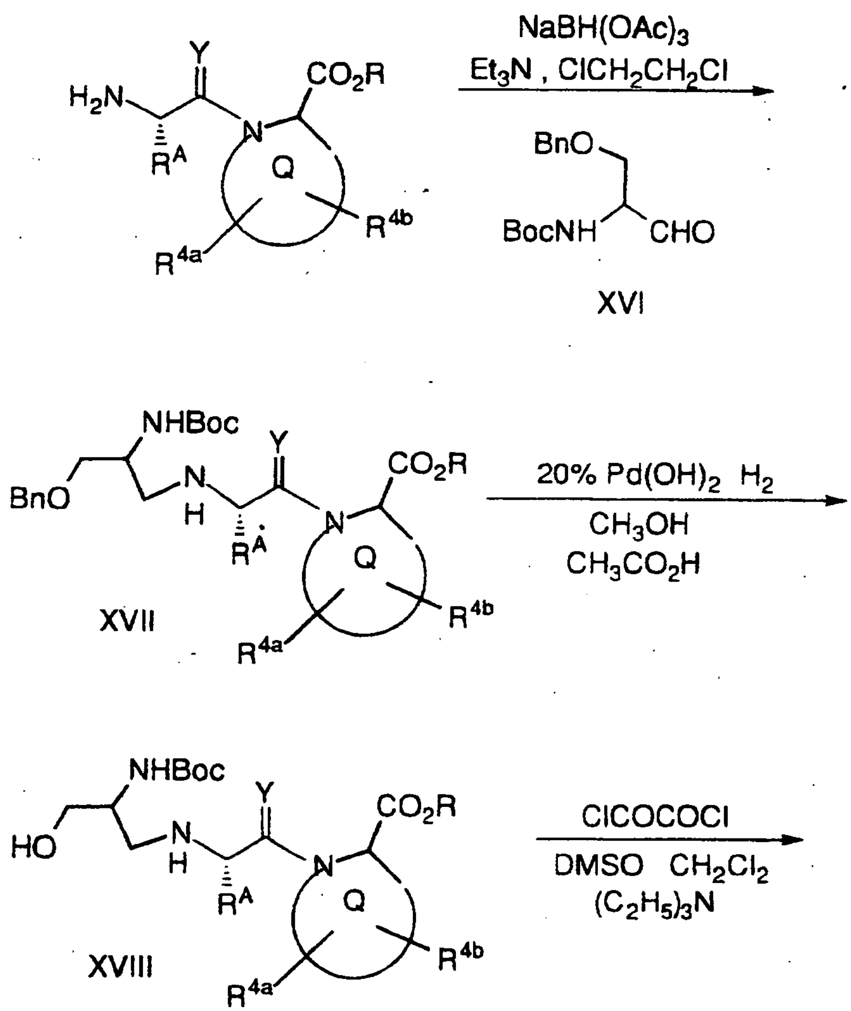


ALTERNATE REACTION SCHEME I FOR COMPOUNDS (II-h) THROUGH (II-o)

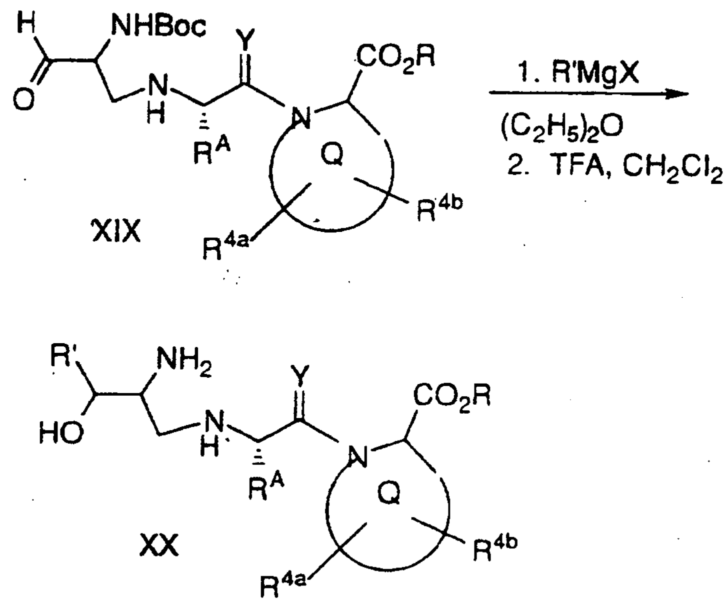


XV

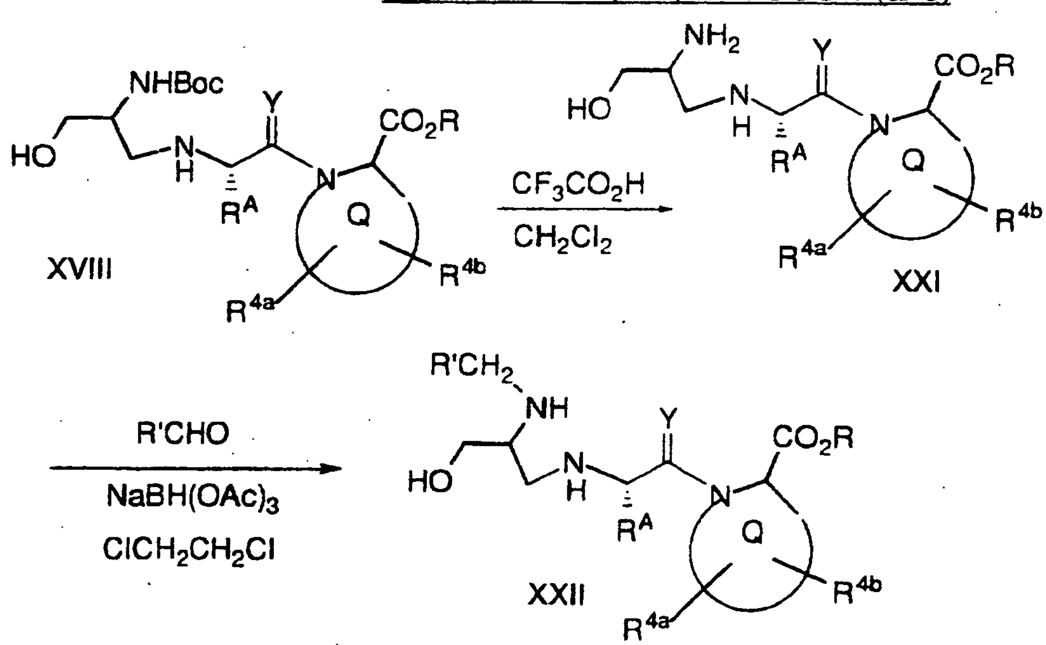
ALTERNATE REACTION SCHEME J FOR COMPOUNDS (II-h) THROUGH (II-o)



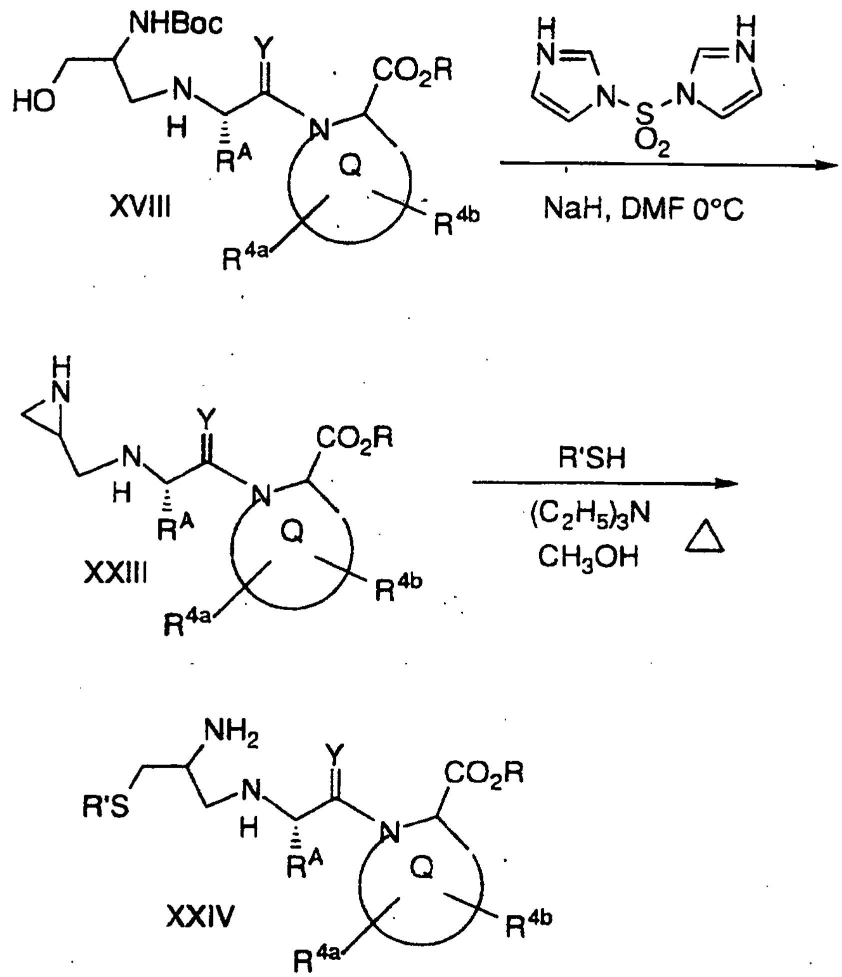
ALTERNATIVE REACTION SCHEME J (continued)



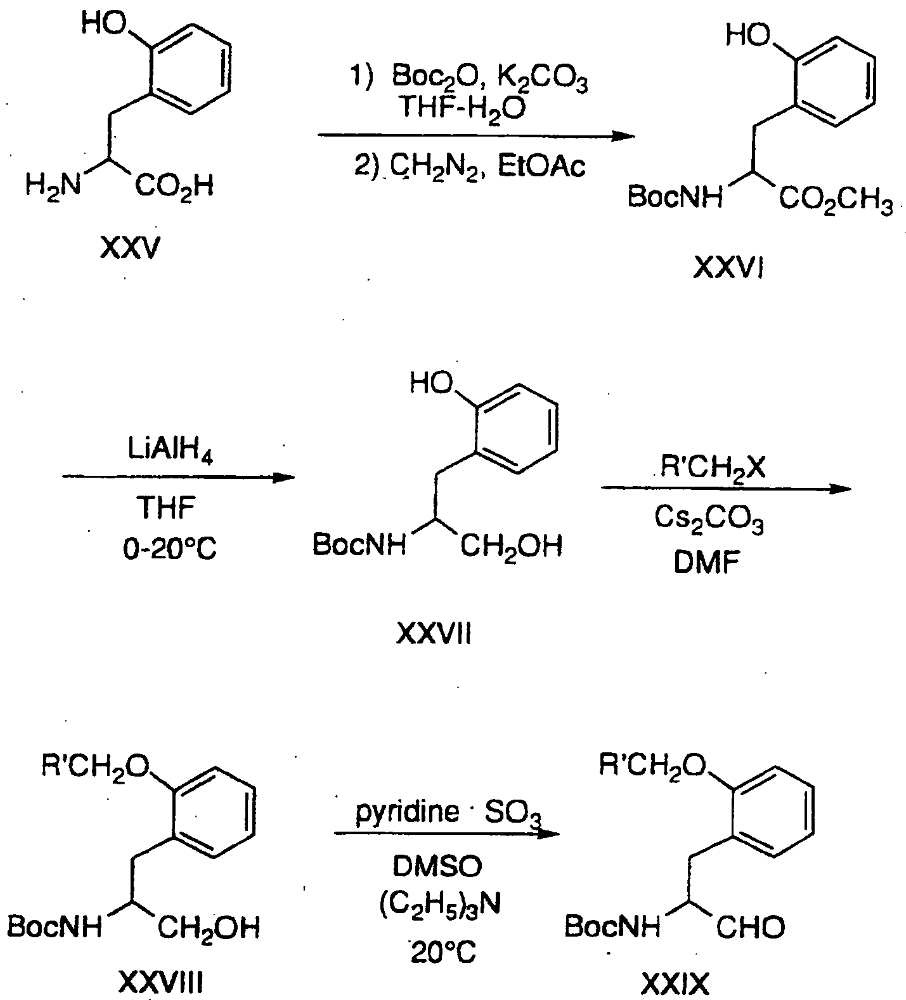
ALTERNATE REACTION SCHEME K FOR COMPOUNDS (II-h) THROUGH (II-o)



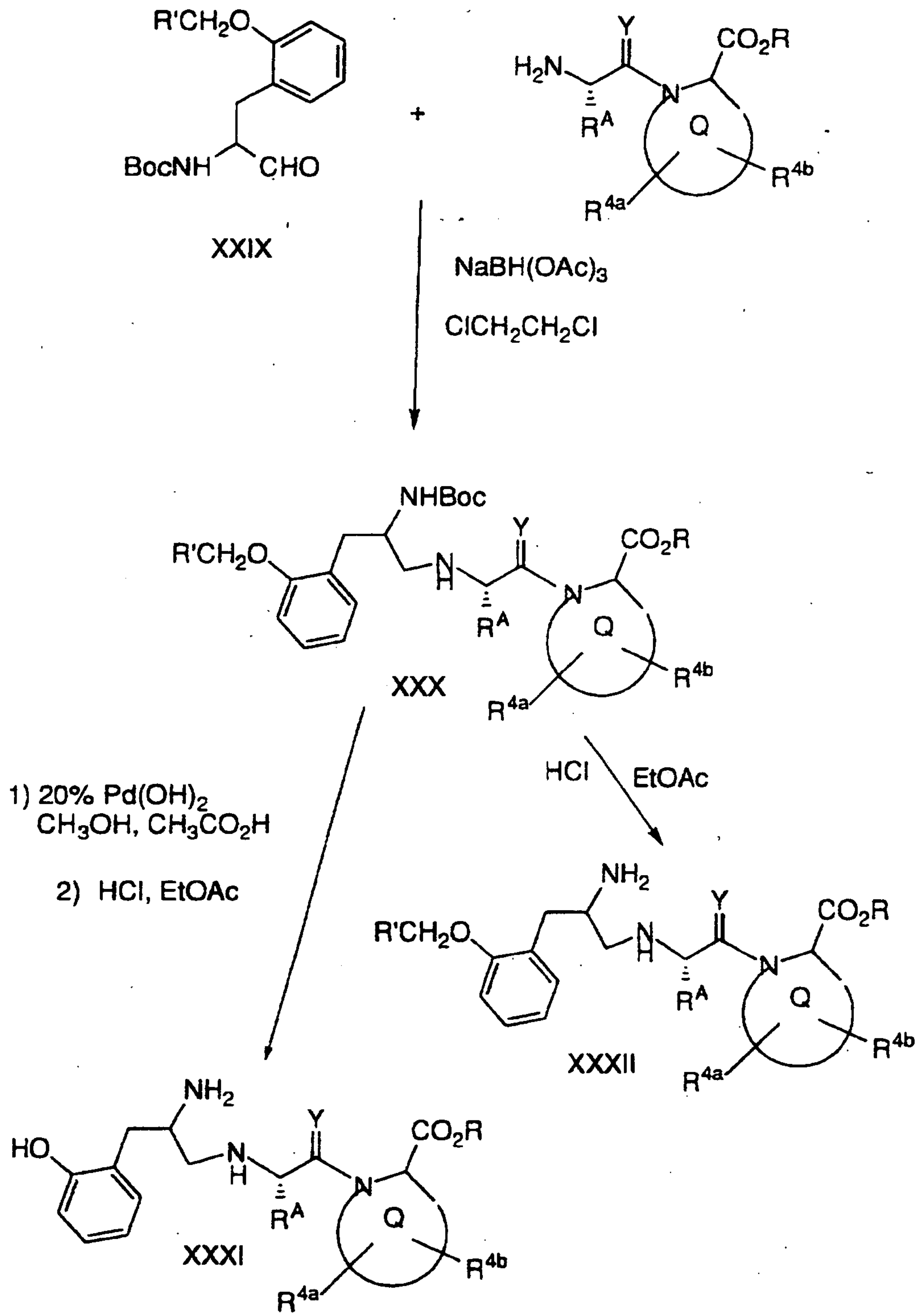
ALTERNATE REACTION SCHEME L FOR COMPOUNDS (II-h) THROUGH (II-o)



ALTERNATE REACTION SCHEME M FOR COMPOUNDS (II-h) THROUGH (II-o)



ALTERNATE REACTION SCHEME M (CONT.)



Certain compounds used in the invention are described below.

EXAMPLE 1

(S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone dihydrochloride

Step A: 1-triphenylmethyl-4-(hydroxymethyl)-imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

Step B: 1-triphenylmethyl-4-(acetoxymethyl)-imidazole

Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder which was sufficiently pure for use in the next reaction.

Step C: 1-(4-cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

A solution of the product from Step B (85.8 g, 225 mmol) and α-bromo-*p*-tolunitrile (50.1 g, 232 mmol) in 500 mL of EtOAc was stirred at 60°C for 20 hours, during which a pale yellow precipitate

formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60°C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60°C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60°C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

Step D: 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole

To a solution of the acetate from Step C (50.4 g, 150 mmol) in 1.5 L of 3:1 THF/water at 0°C was added lithium hydroxide monohydrate (18.9 g, 450 mmol). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. $NaHCO_3$ and brine. The solution was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

Step E: 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde

To a solution of the alcohol from Step D (21.5 g, 101 mmol) in 500 mL of DMSO at room temperature was added triethylamine (56 mL, 402 mmol), then SO_3-pyridine complex (40.5 g, 254 mmol). After 45 minutes, the reaction was poured into 2.5 L of EtOAc, washed with water (4 x 1 L) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the aldehyde as a white powder which was sufficiently pure for use in the next step without further purification.

Step F: (S)-2-(*tert*-butoxycarbonylamino)-*N*-methoxy-*N*-methyl-4-(methylthio)butanamide

L-*N*-Boc-methionine (30.0 g, 0.120 mol), *N,O*-dimethylhydroxylamine hydrochloride (14.1 g, 0.144 mol), EDC hydrochloride (27.7 g, 0.144 mol) and HOBT (19.5 g, 0.144 mol) were stirred in dry DMF (300 mL) at 20°C under nitrogen. More *N,O*-dimethylhydroxylamine hydrochloride (2.3 g, 23 mmol) was added to obtain pH 7-8. The reaction was stirred overnight, the DMF distilled to half the original volume under high vacuum, and the residue partitioned between ethyl acetate and sat. $NaHCO_3$ soln. The organic phase was washed with saturated sodium bicarbonate, water, 10% citric acid, and brine, and dried with sodium sulfate. The solvent was removed *in vacuo* to give the title compound.

Step G: (S)-2-(*tert*-butoxycarbonylamino)-4-(methylthio)butanal

A suspension of lithium aluminum hydride (5.02 g, 0.132 mol) in ether (500 mL) was stirred at room temperature for one hour. The solution was cooled to -50°C under nitrogen, and a solution of the product from Step F (39.8 g, ca. 0.120 mol) in ether (200 mL) was added over 30 min, maintaining the temperature below -40°C. When the addition was complete, the reaction was warmed to 5°C, then recooled to -45°C. Analysis by tlc revealed incomplete reaction. The solution was rewarmed to 5°C, stirred for 30 minutes, then cooled to -50°C. A solution of potassium hydrogen sulfate (72 g, 0.529 mol) in 200 mL water was slowly added, maintaining the temperature below -20°C. The mixture was wasmed to 5°C, filtered through Celite, and concentrated *in vacuo* to provide the title aldehyde.

Step H: (S)-2-(*tert*-butoxycarbonylamino)-*N*-(3-chlorophenyl)-4-(methylthio)butanamine

To a solution of 3-chloroaniline (10.3 mL, 97.4 mmol), the product from Step G (23.9 g, 97.4 mmol), and acetic acid (27.8 mL, 487 mmol) in dichloroethane (250 mL) under nitrogen was added sodium triacetoxyborohydride (41.3 g, 195 mmol). The reaction was

stirred overnight, then quenched with saturated sodium bicarbonate solution. The solution was diluted with $CHCl_3$, and the organic phase was washed with water, 10% citric acid and brine. The solution was dried over sodium sulfate and concentrated *in vacuo* to provide the crude product (34.8 g) which was chromatographed on silica gel with 20% ethyl acetate in hexane to obtain the title compound .

<u>Step I</u>: <u>(S)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[2-(methylthio)ethyl]piperazin-2-one</u>

A solution of the product from Step H (22.0 g, 63.8 mmol) in ethyl acetate (150 mL) was vigorously stirred at 0°C with saturated sodium bicarbonate (150 mL). Chloroacetyl chloride (5.6 mL, 70.2 mmol) was added dropwise, and the reaction stirred at 0°C for 2h. The layers were separated, and the ethyl acetate phase was washed with 10% citric acid and saturated brine, and dried over sodium sulfate. After concentration *in vacuo*, the resulting crude product (27.6 g) was dissolved in DMF (300 mL) and cooled to 0°C under argon. Cesium carbonate (63.9 g, 196 mmol) was added, and the reaction was stirred for two days, allowing it to warm to room temperature. Another portion of cesium carbonate (10 g, 30 mmol) was added, and the reaction was stirred for 16 hours. The DMF was distilled *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic phase was washed with saturated brine, and dried over sodium sulfate. The crude product was chromatographed on silica gel with 20-25% ethyl acetate in hexane to obtain the title compound.

<u>Step J</u>: <u>(S)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[2-(methanesulfonyl)ethyl]piperazin-2-one</u>

A solution of the product from Step I (14.2 g, 37 mmol) in methanol (300 mL) was cooled to 0°C, and a solution of magnesium monoperoxyphthalate (54.9 g, 111 mmol) in 210 mL MeOH was added over 20 minutes. The ice bath was removed, and the solution was allowed to warm to room temperature. After 45 minutes, the reaction was concentrated *in vacuo* to half the original volume, then quenched by

the addition of 2N $Na_2S_2O_3$ soln. The solution was poured into EtOAc and sat $NaHCO_3$ solution, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude sulfone. This material was chromatographed on silica gel with 60-100% ethyl acetate in hexane to obtain the titled compound.

<u>Step K</u>: <u>(S)-1-(3-chlorophenyl)-5-[2-(methanesulfonyl)ethyl]piperazin-2-one</u>

Through a solution of Boc-protected piperazinone from Step J (1.39 g, 3.33 mmol) in 30 mL of EtOAc at 0°C was bubbled anhydrous HCl gas. The saturated solution was stirred for 35 minutes, then concentrated *in vacuo* to provide the hydrochloride salt as a white powder. This material was suspended in EtOAc and treated with dilute aqueous $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc, and the combined organic mixture was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting amine was reconcentrated from toluene to provide the titled material suitable for use in the next step.

<u>Step L</u>: <u>(S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-5-[2-(methanesulfonyl)-ethyl]-2-piperazinone dihydrochloride</u>

To a solution of the amine from Step K (898 mg, 2.83 mmol) and imidazole carboxaldehyde from Step E (897 mg, 4.25 mmol) in 15 mL of 1,2-dichloroethane was added sodium triacetoxyborohydride (1.21 g, 5.7 mmol). The reaction was stirred for 23 hours, then quenched at 0°C with sat. $NaHCO_3$ solution. The solution was poured into $CHCl_3$, and the aqueous layer was back-extracted with $CHCl_3$. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was purified by silica gel chromatography (95:5:0.5-90:10:0 EtOAc:MeOH:NH_4Cl), and the resultant product was taken up in EtOAc/methanol and treated with 2.1 equivalents of 1 M HCl/ether

solution. After concentrated *in vacuo*, the product dihydrochloride was isolated as a white powder.

EXAMPLE 2

1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolyl-methyl]-2-piperazinone dihydrochloride

Step A: N-(3-chlorophenyl)ethylenediamine hydrochloride

To a solution of 3-chloroaniline (30.0 mL, 284 mmol) in 500 mL of dichloromethane at 0°C was added dropwise a solution of 4 N HCl in 1,4-dioxane (80 mL, 320 mmol HCl). The solution was warmed to room temperature, then concentrated to dryness *in vacuo* to provide a white powder. A mixture of this powder with 2-oxazolidinone (24.6 g, 282 mmol) was heated under nitrogen atmosphere at 160°C for 10 hours, during which the solids melted, and gas evolution was observed. The reaction was allowed to cool, forming the crude diamine hydrochloride salt as a pale brown solid.

Step B: *N*-(*tert*-butoxycarbonyl)-*N'*-(3-chlorophenyl)ethylenediamine

The amine hydrochloride from Step A (*ca.* 282 mmol, crude material prepared above) was taken up in 500 mL of THF and 500 mL of sat. aq. $NaHCO_3$ soln., cooled to 0°C, and di-*tert*-butylpyrocarbonate (61.6 g, 282 mmol) was added. After 30 h, the reaction was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled carbamate as a brown oil which was used in the next step without further purification.

Step C: *N*-[2-(*tert*-butoxycarbamoyl)ethyl]-*N*-(3-chlorophenyl)-2-chloroacetamide

A solution of the product from Step B (77 g, *ca.* 282 mmol) and triethylamine (67 mL, 480 mmol) in 500 mL of CH_2Cl_2 was cooled to 0°C. Chloroacetyl chloride (25.5 mL, 320 mmol) was added dropwise, and the reaction was maintained at 0°C with stirring. After 3 h, another portion of chloroacetyl chloride (3.0 mL) was added dropwise. After 30 min, the reaction was poured into EtOAc (2 L) and washed with water, sat. aq. NH_4Cl soln, sat. aq. $NaHCO_3$ soln., and brine. The solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the chloroacetamide as a brown oil which was used in the next step without further purification.

Step D: 4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-2-piperazinone

To a solution of the chloroacetamide from Step C (*ca.* 282 mmol) in 700 mL of dry DMF was added K_2CO_3 (88 g, 0.64 mol). The solution was heated in an oil bath at 70-75°C for 20 hours, cooled to room temperature, and concentrated *in vacuo* to remove *ca.* 500 mL of DMF. The remaining material was poured into 33% EtOAc/hexane, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the product as a brown oil. This material was purified by silica gel chromatography (25-50% EtOAc/hexane) to yield pure product, along with a sample of product (ca. 65% pure by HPLC) containing a less polar impurity.

Step E: 1-(3-chlorophenyl)-2-piperazinone

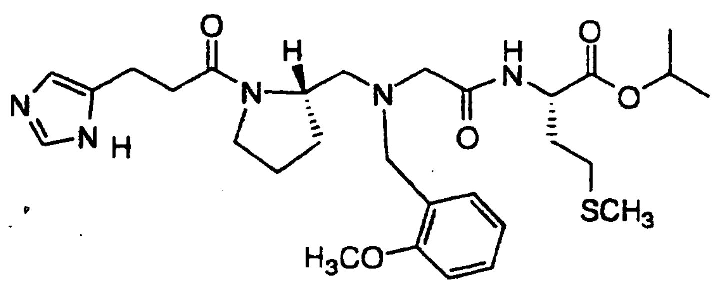
Through a solution of Boc-protected piperazinone from Step D (17.19 g, 55.4 mmol) in 500 mL of EtOAc at -78°C was bubbled anhydrous HCl gas. The saturated solution was warmed to 0°C, and stirred for 12 hours. Nitrogen gas was bubbled through the reaction to remove excess HCl, and the mixture was warmed to room temperature. The solution was concentrated *in vacuo* to provide the hydrochloride as a white powder. This material was taken up in 300 mL of CH_2Cl_2 and

treated with dilute aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 (8 x 300 mL) until tlc analysis indicated complete extraction. The combined organic mixture was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled free amine as a pale brown oil.

Step F: 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolylmethyl]-2-piperazinone dihydrochloride

To a solution of the amine from Step E (55.4 mmol, prepared above) in 200 mL of 1,2-dichloroethane at 0°C was added 4Å powdered molecular sieves (10 g), followed by sodium triacetoxyborohydride (17.7 g, 83.3 mmol). The imidazole carboxaldehyde from Step E of Example 1 (11.9 g, 56.4 mmol) was added, and the reaction was stirred at 0°C. After 26 hours, the reaction was poured into EtOAc, washed with dilute aq. $NaHCO_3$, and the aqueous layer was back-extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was taken up in 500 mL of 5:1 benzene:CH_2Cl_2, and propylamine (20 mL) was added. The mixture was stirred for 12 hours, then concentrated *in vacuo* to afford a pale yellow foam. This material was purified by silica gel chromatography (2-7% $MeOH/CH_2Cl_2$), and the resultant white foam was taken up in CH_2Cl_2 and treated with 2.1 equivalents of 1 M HCl/ether solution. After concentrated *in vacuo*, the product dihydrochloride was isolated as a white powder.

EXAMPLE 3



N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester

Step A: 2-Methoxybenzylglycine methyl ester

2-Methoxybenzyl alcohol (53.5 g, 0.39 mol) was dissolved in CH_2Cl_2 (200 mL), treated with diisopropylethylamine (81 mL, 0.74 mol), cooled to 0°C. with stirring in an ice-CH_3OH bath under Ar, and treated dropwise with methanesulfonyl chloride (33 mL, 0.43 mol). After 0.5 hr, the reaction mixture was left to warm to ambient temperature and stirred for 4 hr. This solution and diisopropylethylamine (202.5 mL, 1.16 mol) were added alternately portionwise with to a slurry of glycine methyl ester hydrochloride (146.5 g, 1.17 mol) in DMF (250 mL) with stirring at 0°C. The reaction mixture was left to stir and warm to room temperature overnight. The DMF was removed under reduced pressure, and the residue was partitioned between EtOAc (1 L) and satd $NaHCO_3$ solution (1 L). The aqueous layer was washed with EtOAc (2 x 600 mL), the organics combined, washed with brine and dried ($MgSO_4$). Filtration and concentration to dryness gave the title compound after chromatography (SiO_2, 1-5% CH_3OH/CH_2Cl_2).

Step B: N-[(2S)-(t-Butoxycarbonylpyrrolidinyl-methyl)-N-(2-methoxybenzyl)glycine methyl ester

2-Methoxybenzylglycine methyl ester (27.4 g, 0.131 mol) was dissolved in 1,2-dichloroethane (500 ml), 3Å molecular sieves (20 g) were added, and the pH of the reaction mixture adjusted to pH 5 with acetic acid (7.5 mL, 0.131 mol). N-(t-Butoxycarbonyl)-L-prolinal (26.1 g, 0.131 mol) (J. Org. Chem. (1994) **59**, [21], 6287-95) was added followed by sodium triacetoxyborohydride (33.2 g, 0.157 mol). The mixture was stirred at ambient temperature for 18 h, filtered through celite and concentrated. The residue was partitioned between EtOAc and sat. $NaHCO_3$ (500 ml/100 ml). The aqueous layer was washed with EtOAc (3x100 ml). The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated to give the title compound.

Step C: N-[(2S)-(t-Butoxycarbonylpyrrolidinyl-methyl)-N-(2-methoxybenzyl)glycine

N-[(2S)-(t-Butoxycarbonylpyrrolidinylmethyl)-N-(2-methoxybenzyl)glycine methyl ester (7.0 g, 0.018 mol) was dissolved in CH_3OH (150 ml) and 1N NaOH (71 ml, 0.071 mol) was added with cooling in an ice-water bath. The mixture was stirred at ambient temperature for 2 hr, neutralized with 1N HCl (71 ml, 0.071 mol), concentrated to remove the CH_3OH, and the residue extracted with EtOAc (3x200 mL). The organic layers were combined, dried with Mg_2SO_4, filtered, and concentrated to give the title compound as a foam.

Step D: Methionine isopropyl ester hydrochloride

N-(t-Butoxycarbonyl)methionine (25 g, 0.1 mol), isopropyl alcohol (11.8 mL, 0.15 mol), EDC (21.1 g, 0.11 mol), and 4-dimethyl-aminopyridine (DMAP) (1.22 g, 0.01 mol) were dissolved in CH_2Cl_2 (400 mL) with stirring in an ice-water bath. After 2 h the bath was removed, and the solution was left to stir o.n. at RT. The reaction mixture was concentrated to dryness, then partitioned between EtOAc and H_2O, the aqueous layer washed with EtOAc (2 x 50 mL), the organics combined, washed with $NaHCO_3$ soln, brine, and dried (Na_2SO_4). Filtration and concentration to dryness gave a yellow oil after chromatography (flash silica gel column, hexane: EtOAc, 6:1 to 5:1).

N-(t-Butoxycarbonyl)methionine isopropyl ester (20.5 g, 0.07 mol) was dissolved in EtOAc (200 mL) with stirring and cooling to -20°C in a dry ice- acetone bath. HCl gas was bubbled into the solution for 10 min, the flask was stoppered and stirred for 1 h. Tlc (EtOAc: hexane, 1:3) indicates loss of starting material. Argon was bubbled through the soln for 5 min, then it was concentrated to dryness to give the title compound as a white solid.

Step E: N-[(2S)-(t-Butoxycarbonylpyrrolidinyl-methyl)-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester

N-[(2S)-(t-Butoxycarbonylpyrrolidinylmethyl)-N-(2-methoxybenzyl)glycine (from step C) (5.98 g, 0.0158 mol), dissolved in CH_2Cl_2 (100 mL), was treated with HOBT (2.57 g, 0.019 mol), EDC (4.54 g, 0.024 mol), and methionine isopropyl ester hydrochloride (4.33 g, 0.019 mol). The pH was adjusted to 7.5 with Et_3N (8.81 mL, 0.063 mol) and the mixture was stirred at ambient temperature for 18 h. The mixture was diluted with EtOAc (150 mL) and washed sequentially with 10% citric acid soln, saturated $NaHCO_3$ solution, brine, and dried ($MgSO_4$). Filtration and concentration to dryness gave the title compound as a thick oil. This was used without further purification.

Step F: N-((2S)-Pyrrolidinylmethyl)-N-(2-methoxybenzyl)-glycyl-methionine isopropyl ester bis hydrochloride

N-[(2S)-(t-Butoxycarbonylpyrrolidinylmethyl)-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester (0.85 g, 1.54 mmol) was dissolved in EtOAc (25 mL) and cooled to 0°C. HCl was bubbled through the mixture until the soln was saturated, and it was stoppered and stirred for 3 hr. Argon was bubbled through the mixture to remove excess HCl and the mixture was then concentrated to give the title compound.

Step G: N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester

N-((2S)-Pyrrolidinylmethyl)-N-(2-methoxybenzyl)glycyl methionine isopropyl ester bis hydrochloride (0.800 g, 1.53 mmol), dissolved in DMF (30 mL), was treated with 1H-imidazol-4-propionic acid (0.43 g, 3.05 mmol) (prepared by catalytic hydrogenation of urocanic acid in 20% acetic acid with Pd on carbon), and BOP reagent (1.35 g, 3.05 mmol). The pH was adjusted to 7.5 with N-methyl-morpholine (0.756 mL, 6.89 mmol), and the mixture was stirred at ambient temperature for 18 h. The mixture was concentrated to

dryness, diluted with EtOAc (100 mL), washed with 5% Na_2CO_3 solution, brine, and dried ($MgSO_4$). Filtration and concentration to dryness gave an oil which was purified by chromatography (silica gel, 95:5 CH_2Cl_2/MeOH) to give the title compound as a foam.

^1H NMR (CD_3OD); δ 7.58 (d, 1H, J=1 Hz), 7.25-7.31 (m, 2H), 6.89-7.00 (m, 2H), 6.81 (s, 1H), 5.00-5.06 (m, 1H), 4.49-4.56 (m, 1H), 4.23-4.30 (m, 1H), 3.91 (d, 1H, J=13 Hz), 3.86 (s, 3H), 3.54 (d, 1H, J=13Hz), 3.30-3.41 (m, 2H), 3.36 (d, 1H, J=17 Hz), 3.15 (d, 1H, J=17 Hz), 2.85-2.92 (m, 2H), 2.56-2.77 (m, 3H), 2.30-2.45 (m, 3H), 2.05-2.17 (m, 1H), 2.04 (s, 3H), 1.69-1.86 (m, 5H), 1.24 (d, 6H, J=6 Hz).

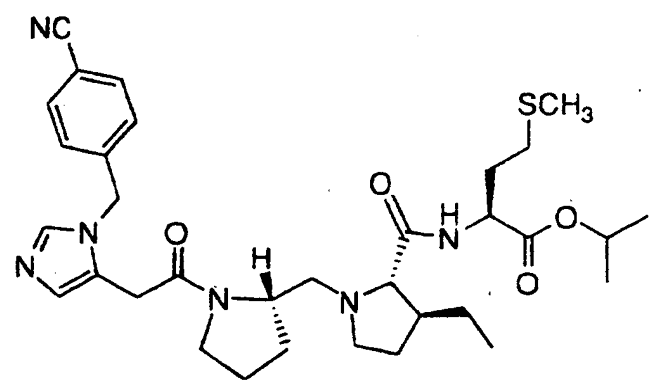
Anal. calculated for $C_{29}H_{43}N_5O_5S \cdot 0.6\ H_2O$:

C, 59.59; H, 7.62; N, 11.98;

Found: C, 59.58; H, 7.43; N, 12.02.

EXAMPLE 4

(N-[1-Cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester



Step A: Diethyl 1-Acetyl-5-hydroxy-3-ethylpyrrolidine-2,2-dicarboxylate

Sodium (4.02 g, 0.175 mol) was dissolved in a stirred solution of diethyl acetamidomalonate (235.4 g, 1.19 mol) in abs EtOH (1.4 L) at ambient temperature under argon. The reaction mixture was cooled to 0°C, and trans-2-pentenal (100 g, 1.08 mol) was

added dropwise maintaining the reaction temperature at <5°C. After the addition, the reaction was allowed to warm to room temperature, stirred for 4 h, then quenched with acetic acid (28 mL). The solution was concentrated *in vacuo*, and the residue dissolved in EtOAc (1.5 L), washed with 10% $NaHCO_3$ solution (2 x 300 mL), brine, and dried ($MgSO_4$). The solution was filtered and concentrated to 700 mL, then heated to reflux and treated with hexane (1 L). On cooling, the title compound precipitated and was collected, mp 106 - 109°C. ^1H NMR (CD_3OD) δ 5.65 (d, 1H, J= 5 Hz), 4.1 - 4.25 (m, 4H), 2.7-2.8 (m, 1H), 2.21 (s, 3H), 2.10 (dd, 1H, J = 6, 13, Hz),1.86- 1.97 (m, 2H), 1.27 (t, 3H, J= 7 Hz), 1.23 (t, 3H, J= 7 Hz), 1.1- 1.25 (m, 1H), 0.97 (t, 3H, J= 7 Hz).

Step B: <u>Diethyl 1-Acetyl-3-ethylpyrrolidine-2,2-dicarboxylate</u>

To a solution of diethyl 1-acetyl-5-hydroxy-3-ethyl-pyrrolidine-2,2-dicarboxylate (287 g, 0.95 mol) and triethylsilane (228 mL, 1.43 mol) in CH_2Cl_2 (3 L) under argon was added trifluoroacetic acid (735 mL, 9.53 mol) dropwise with stirring while maintaining the internal temperature at 25°C by means of an ice bath. After stirring for 3 h at 23°C, the solution was concentrated *in vacuo*, , the residue diluted with CH_2Cl_2 (1.5 L), then treated with H_2O (1 L) and solid Na_2CO_3 with vigorous stirring until the solution was basic. The organic layer was separated, dried (Na_2SO_4), filtered, then concentrated to give the title compound as a yellow oil which was used without further purification.

Step C: <u>3-Ethylproline hydrochloride (Cis:Trans Mixture)</u>

Diethyl 1-acetyl-3-ethylpyrrolidine-2,2-dicarboxylate (373 g, 0.95 mol) was suspended in 6N HCl (2 L) and HOAc (500 mL) and heated at reflux for 20 h. The reaction mixture was cooled, washed with EtOAc (1L), then concentrated *in vacuo* to give an oil which crystallized upon trituration with ether to give the title compound. ^1H NMR (D_2O) δ 4.23 (d, 1H, J= 8 Hz), 3.84 (d, 1H, J= 8 Hz), 3.15-3.4 (m, 4H), 2.33- 2.44 (m, 1H), 2.19-2.4 (m, 1H), 2.02- 2.15 (m, 2H),

1.53- 1.72 (m, 3H), 1.23- 1.43 (m, 2H), 1.0- 1.15 (m, 1H), 0.75 - 0.83 (m, 6H).

Step D: N-[(*tert*-Butyloxy)carbonyl]-*cis:trans*-3-ethylproline methyl ester

3-Ethylproline hydrochloride (Cis:Trans Mixture) (20 g, 0.11 mol) was dissolved in CH_3OH (200 mL), and the solution was saturated with HCl gas, then stirred at 23°C for 24 h. Argon was bubbled through the solution to remove excess HCl. The solution was treated with $NaHCO_3$ (>84 g) to a pH of 8, then di-*tert*-butyl dicarbonate (25.1 g, 0.115 mol) dissolved in CH_3OH (20 mL) was added slowly. After stirring for 18 h at 23°C, the mixture was filtered, the filtrate concentrated, and the residue triturated with EtOAc, filtered again, and concentrated to give the title compound as an oil.

Step E: N-[(*tert*-Butyloxy)carbonyl]-*trans*-3-ethylproline and N-[(*tert*-Butyloxy)carbonyl]-*cis*-3-ethylproline methyl ester

N-[(*tert*-Butyloxy)carbonyl]-*cis,trans*-3-ethylproline methyl ester (29.1 g, 0.113 mol) was dissolved in CH_3OH (114 mL) with cooling to 0°C, then treated with 1 N NaOH (114 mL). After stirring for 20 h at 23°C, the solution was concentrated to remove the CH_3OH and then extracted with EtOAc (3 x). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to give 12.8 g of N-[(*tert*-Butyloxy)carbonyl]-*cis*-3-ethylproline methyl ester as an oil. The aqueous layer was acidified with solid citric acid and extracted with EtOAc (2 x), the organic layers combined, dried ($MgSO_4$), filtered, and concentrated to give N-[(*tert*-Butyloxy)carbonyl]-*trans*-3-ethylproline as an oil. ^1H NMR (CD_3OD) δ 3.86 and 3.78 (2 d, 1H, J = 6 Hz), 3.33 - 3.58 (m, 2H), 2.01 - 2.22 (m, 2H), 1.5 - 1.74 (m, 2H), 1.33 - 1.5 (m, 1H), 1.45 and 1.42 (2 s, 9H), 0.98 (t, 3H, J= 8 Hz).

Step F: <u>3(S)-Ethyl-2(S)-proline hydrochloride</u>

N-[(*tert*-Butyloxy)carbonyl]-*trans*-3-ethylproline (15.5 g, 0.064 mol), S-α-methylbenzylamine (9.03 mL, 0.070 mol), HOBT (10.73 g, 0.70 mol), and N-methylmorpholine (8 mL, 0.076 mol) were dissolved in CH_2Cl_2 (150 mL) with sitrring in an ice-H_2O bath, treated with EDC (13.4 g, 0.070 mol) stirred at 23°C for 48 h. The reaction mixture was partitioned between EtOAc and 10% citric acid solution, the organic layer washed with satd $NaHCO_3$ solution, brine and dried ($MgSO_4$), filtered, and concentrated to give an oil. This oil was dissolved in a minimum amount of ether (10 mL) to crystallize the desired S,S,S diastereomer (4.2 g), mp 118-121°C. A solution of this product in 8N HCl (87 mL) and glacial acetic acid (22 mL) was heated at reflux overnight. The solution was concentrated on a rotary evaporator, and the residue taken up in H_2O and extracted with ether. The aqueous layer was concentrated to dryness to give a 1:1 mixture of 3(S)-ethyl-2(S)-proline hydrochloride and α-methylbenzylamine.

3(S)-Ethyl-2(S)-proline containing α-methylbenzylamine (2.0 g, 0.0128 mol) was dissolved in dioxane (10 mL) and H_2O (10 mL) with stirring and cooling to 0°C. N,N-diisopropylethylamine (2.2 mL, 0.0128 mol) and di-*tert*-butyl-dicarbonate (2.79 g, 0.0128 mol) were added and stirring was continued at 23°C for 48 h. The reaction mixture was partitioned between EtOAc (60 mL) and H_2O (30 mL), the organic layer washed with 0.5N NaOH (2 x 40 mL), the aqueous layers combined and washed with EtOAc (30 mL) and this layer back-extracted with 0.5 N NaOH (30 mL). The aqueous layers were combined and carefully acidified at 0°C with 1N HCl to pH 3. This mixture was extracted with EtOAc (3 x 40 mL), the organics combined, dried ($MgSO_4$), filtered and concentrated to give N-[(*tert*-Butyloxy) carbonyl-3(S)-ethyl-2(S)-proline as a colorless oil. N-[(*tert*-Butyloxy) carbonyl-3(S)-ethyl-2(S)-proline was dissolved in EtOAc (50 mL) and the solution was saturated with HCl gas with cooling in an ice-H_2O bath. The solution was stoppered and stirred at 0°C. for 3 hr. Argon was bubbled through the solution to remove excess HCl, and the solution was concentrated to dryness to give 3(S)-ethyl-2(S)-proline hydrochloride.

Step G: N-(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-proline

3(S)-Ethyl-2(S)-proline hydrochloride (2.33 g, 0.013 mol) was dissolved in CH_3OH (20 mL), treated with 3A molecular sieves (2 g) and KOAc (1.27 g, 0.013 mol) to adjust the pH of the reaction mixture to 4.5-5, then N-[(*tert*-Butyloxy)carbonyl-prolinal (Pettit et al., J. Org. Chem. (1994) **59**, [21] 6287-95) (3.36 g, 0.017 mol) was added, and the mixture was stirred for 16 hrs at room temperature. The reaction mixture was filtered, quenched with aq satd $NaHCO_3$ (5 mL) and concentrated to dryness. The residue was extracted with $CHCl_3$. The extract was dried ($MgSO_4$), filtered, and concentrated to give the title compound and inorganic salts.

Step H: N-(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester

N-(t-Butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-proline (2.4 g, 0.008 mol), methionine isopropyl ester hydrochloride (2.21 g, 0.0097 mol), HOBT (1.49 g, 0.0097 mol) and EDC (1.86 g, 0.0097 mol) were dissolved in DMF (15 mL) at room temperature and treated with N-methylmorpholine (3 mL, 0.024 mol). The reaction mixture was stirred overnight at room temperature, then concentrated and partitioned between EtOAc and H_2O. The organic layer was washed with aq satd $NaHCO_3$ solution, brine, and dried ($MgSO_4$). The crude product was chromatographed on a flash silica gel column eluting with hexane: EtOAc, 7:3 to give N-(t-butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester.

Step I: Pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester hydrochloride

N-(t-butyloxycarbonyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester (1.38 g, 0.0028 mol) was dissolved in EtOAc (40 mL), cooled to -20°C, saturated with HCl gas,

and stirred at 0°C. for 1.25 hr, and room temperature for 0.25 hr. Concentration to dryness gave pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester hydrochloride.

Step J: Preparation of 1H-Imidazole-4- acetic acid methyl ester hydrochloride

A solution of 1H-imidazole-4-acetic acid hydrochloride (4.00g, 24.6 mmol) in methanol (100 ml) was saturated with gaseous hydrogen chloride. The resulting solution was allowed to stand at room temperature (RT) for 18hr. The solvent was evaporated in vacuo to afford the title compound as a white solid.

^{1}H NMR($CDCl_3$, 400 MHz) δ 8.85(1H, s),7.45(1H, s), 3.89(2H, s) and 3.75(3H, s) ppm.

Step K: Preparation of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester

To a solution of 1H-Imidazole-4- acetic acid methyl ester hydrochloride (24.85g, 0.141mol) in dimethyl formamide (DMF) (115ml) was added triethylamine (57.2 ml, 0.412 mol) and triphenyl-methyl bromide(55.3g, 0.171mol) and the suspension was stirred for 24hr. After this time, the reaction mixture was diluted with ethyl acetate (EtOAc) (1 l) and water (350 ml). The organic phase was washed with sat. aq. $NaHCO_3$ (350 ml), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (SiO_2, 0-100% ethyl acetate in hexanes; gradient elution) to provide the title compound as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35(1H, s), 7.31(9H, m), 7.22(6H, m), 6.76(1H, s), 3.68(3H, s) and 3.60(2H, s) ppm.

Step L: Preparation of [1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester

To a solution of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester (8.00g, 20.9mmol) in acetonitrile (70 ml) was added bromo-p-toluonitrile (4.10g, 20.92 mmol) and heated at 55°C

for 3 hr. After this time, the reaction was cooled to room temperature and the resulting imidazolium salt (white precipitate) was collected by filtration. The filtrate was heated at 55°C for 18hr. The reaction mixture was cooled to room temperature and evaporated in vacuo. To the residue was added EtOAc (70 ml) and the resulting white precipitate collected by filtration. The precipitated imidazolium salts were combined, suspended in methanol (100 ml) and heated to reflux for 30min. After this time, the solvent was removed in vacuo, the resulting residue was suspended in EtOAc (75ml) and the solid isolated by filtration and washed (EtOAc). The solid was treated with sat aq $NaHCO_3$ (300ml) and CH_2Cl_2 (300ml) and stirred at room temperature for 2 hr. The organic layer was separated, dried ($MgSO_4$) and evaporated in vacuo to afford the title compound as a white solid : ^{1}HNMR($CDCl_3$, 400 MHz) δ 7.65(1H, d, J=8Hz), 7.53(1H, s), 7.15(1H, d, J=8Hz), 7.04(1H, s), 5.24(2H, s), 3.62(3H, s) and 3.45(2H, s) ppm.

Step M: Preparation of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid

A solution of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester (4.44g, 17.4mmol) in THF (100ml) and 1 M lithium hydroxide (17.4 ml, 17.4 mmol) was stirred at RT for 18 hr. 1 M HCl (17.4 ml) was added and the THF was removed by evaporation in vacuo. The aqueous solution was lyophilized to afford the title compound containing lithium chloride as a white solid.
^{1}H NMR(CD_3OD, 400 MHz) δ 8.22(1H, s), 7.74(1H, d, J=8.4Hz), 7.36(1H, d, J=8.4Hz), 7.15(1H, s), 5.43(2H, s) and 3.49(2H, s) ppm.

Step N: Preparation of N-[(1-(4-Cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester

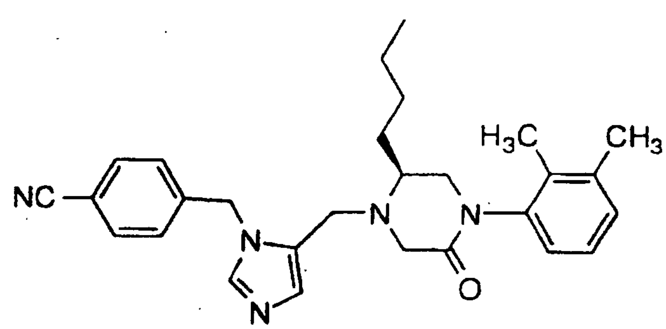
[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid • LiCl (0.416 g, 1.47 mmol), pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester hydrochloride (Step I) (0.63 g, 1.33 mmol), HOOBT (0.239 g, 1.47 mmol), and EDC (0.281 g, 1.47 mmol) were

dissolved in degassed DMF (20 mL) with stirring at room temperature, N-methylmorpholine (0.8 mL, 5.32 mmol) was added to achieve a pH of 7, and stirring was continued overnight. The reaction mixture was concentrated to remove most of the DMF, and the residue was partitioned between EtOAc and aq satd $NaHCO_3$ solution. The aq layer was washed with EtOAc, the organics combined, washed with brine and dried ($MgSO_4$). Filtration and concentration to dryness gave the title compound after chromatography on silica gel eluting with CH_2Cl_2:CH_3OH, 95:5.

Anal. calcd for $C_{33}H_{46}N_6O_4S \cdot 0.7\ H_2O$:
C, 62.38; H, 7.52; N, 13.23;
Found: C, 62.40; H, 7.17; N, 13.11.
FAB MS 623 (M+1)

EXAMPLE 5

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one



1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one ditrifluoroacetic acid salt

Step A: N-Methoxy-N-methyl 4-benzyloxy-2(S)-(*tert*-butoxycarbonylamino)butanamide

4-Benzyloxy-2(S)-(*tert*-butoxycarbonylamino)butanoic acid (1.00 g, 3.23 mmol) was converted to the title compound following the

procedure described in Example 24, Step A, using EDC · HCl (0.680 g, 3.55 mmol). HOBT (0.436 g, 3.23 mmol) and N,O-dimethylhydroxylamine hydrochloride (0.473 g, 4.85 mmol) in DMF (50 mL) at pH 7. After workup, the title compound was obtained as a clear gum.

Step B: 4-(1-Benzyloxyethyl)-2(S)-(*tert*-butoxycarbonylamino) butanal

The title compound was obtained by lithium aluminum hydride reduction of the product of Step A using the procedure described in Example 24, Step B.

Step C: N-(2,3-Dimethylphenyl)-4-(2-benzyloxyethyl)-2-(S)-(*tert*-butoxycarbonylamino)butanamine

The title compound was prepared from the product of Step C according to the procedure described in Example 24, Step C, using 2,3-dimethylaniline (0.505 mL, 4.14 mmol), sodium triacetoxyborohydride (1.20 g, 5.65 mmol) and crushed molecular sieves (1 g) at pH 5 in dichloroethane (20 mL). The title compound was obtained after purification on silica gel, eluting with 15% ethyl acetate in hexane.

Step D: 2(S)-(2-Benzyloxyethyl)-1-*tert*-butoxycarbonyl-4-(2,3-dimethylphenyl)piperazin-5-one

The title compound was prepared from the product of Step C according to the procedure described in Example 24, Step D, using chloroacetyl chloride (0.21 mL, 2.57 mmol) in 60 mL 1:1 ethyl acetate:saturated sodium bicarbonate, followed by reaction of the crude product with sodium hydride (0.373 g, 60% dispersion in oil, 9.32 mmol) in DMF (30 mL). After workup, the crude product was chromatographed on silica gel with 30% ethyl acetate in hexane to obtain the title compound.

Step E: 1-*tert*-Butoxycarbonyl-4-(2,3-dimethylphenyl)-2(S)-(2-hydroxyethyl)piperazin-5-one

The product from Step D was dissolved in methanol (40 mL) and 10% Pd/C was added (0.160 g). The reaction was shaken under 60 psi hydrogen overnight. The catalyst was removed by filtration, and the solvent evaporated to give the title compound.

Step F: 1-*tert*-Butoxycarbonyl-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one

The product from Step E (0.241 g, 0.688 mmol) was dissolved in DMF (10 mL) containing methyl iodide (0.21 mL, 3.44 mmol) and the stirred solution cooled to 0°C under nitrogen. Sodium hydride (0.070 g, 60% dispersion in oil, 1.72 mmol) was added and the reaction stirred for 1h. The reaction was quenched with water, and the DMF removed under vacuum. The residue was partitioned between ethyl acetate and water, and the organic phase washed with saturated brine and dried over magnesium sulfate. The crude product was chromatographed on silica gel with 40% ethyl acetate in hexane to give the title compound.

Step G: 4-(2,3-Dimethylphenyl)-2(S)-(2-methoxyethyl)-1-[4-(1-triphenylmethylimidazolyl)methyl]piperazin-5-one

The product from Step F (0.113 g, 0.312 mmol) was converted to the title compound according to the procedure described in Example 24, Step E, except using 30% trifluoroacetic acid in dichloromethane (10 mL) for 1 h for the initial deprotection. The volatiles were removed *in vacuo*, and the residue dissolved in dichloroethane. Triethylamine was added to obtain pH 5. Sodium triacetoxyborohydride (0.100 g, 0.468 mmol) and 1-triphenylmethyl-4-imidazolylcarboxaldehyde (0.1164 g, 0.343 mmol) was added. The reaction was stirred overnight at 20°C then poured into saturated sodium bicarbonate solution. The organic phase was washed with

saturated brine and dried over magnesium sulfate. Silica gel chromatography using 5% methanol in chloroform as eluant yielded the title compound.

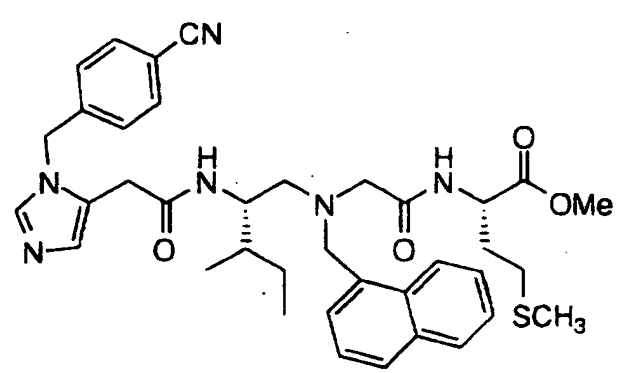
Step H: 1-[1-(4-Cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one ditrifluoroacetic acid salt

The product from Step G (0.182 g, 0.312 mmol) was converted to the title compound according to the procedure described in Example 25, using 4-cyanobenzylbromide (0.061 g, 0.312 mmol) in acetonitrile (10 mL), followed by reaction of the crude imidazolium salt with triethylsilane (0.13 mL) and trifluoroacetic acid (2 mL) in dichloromethane (6 mL). Purification was accomplished by reverse phase preparative HPLC with a mixed gradient of 0%-70% acetonitrile/0.1% TFA; 100%-30% 0.1% aqueous TFA over 60 min. The title compound was isolated after lyophilization from water. FAB ms (m+1) 458.

Anal. Calc. for $C_{27}H_{31}N_5O_2 \cdot 0.35\ H_2O \cdot 2.0\ TFA$:
C, 53.81; H, 4.91; N, 10.21.
Found: C, 53.83; H, 4.95; N, 10.29.

EXAMPLE 6

N-[2(S)-N'-(1-(4-Cyanophenyl-methyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester



Preparation of N-[2(S)-N'-(1-(4-Cyanophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine bis trifluoroacetate

Step A: Preparation of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester (**23**)

To a suspension of 1H-imidazole-4-acetic acid methyl ester hydrochloride (**1**, 7.48, 42.4 mmol) in methylene chloride (200 ml) was added triethylamine (17.7 ml, 127 mmol) and triphenylmethyl bromide (16.4 g, 50.8 mmol) and stirred for 72 h. After this time, reaction mixture was washed with sat. aq. sodium bicarbonate (100 ml) and water (100 ml). The organic layer was evaporated *in vacuo* and purified by flash chromatography (30-100% ethyl acetate/hexanes gradient elution) to provide **23** as a white solid.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (1H, s), 7.31 (9H, m), 7.22 (6H, m), 6.76 (1H, s), 3.68 (3H, s) and 3.60 (2H, s) ppm.

Step B: Preparation of 1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid methyl ester (**16**)

To a solution of 1-(triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester (**23**, 274 mg, 0.736 mmol) in acetonitrile (10 ml) was added 4-nitrobenzylbromide (159 mg, 0.736 mmol) and heated to 55°C for 16 h. After this time, the reaction was cooled to room temperature, treated with ethyl acetate (20 ml) and the resulting precipitate was filtered. The filtrate was concentrated to dryness *in vacuo* and the residue was redissolved in acetonitrile (4 ml) and heated to 65°C for 3 h. After this time, the reaction mixture was evaporated to dryness and combined with initial precipitate. This residue was dissolved in methanol (5 ml) and heated to reflux for 30 min. The resulting solution was evaporated in vacuo and the residue was purified by flash chromatography (2-5% methanol/methylene chloride gradient elution) to provide **16**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (2H, d, J=8.8 Hz), 7.53 (1H, s), 7.19 (2H, d, J=8.8 Hz), 7.03 (1H, s), 5.28 (2H, s), 3.61 (3H, s) and 3.44 (2H, s) ppm.

Step C: 1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid hydrochloride

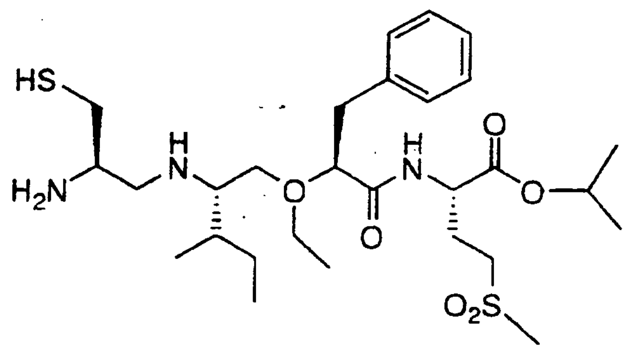
1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetic acid methyl ester (0.115 g, 0.42 mmol) was dissolved in 1.0N hydrochloric acid (10 ml) and heated at 55°C for 3 h. The solution was evaporated *in vacuo* to give the compound as a white solid.
^{1}H NMR (CD_3OD, 400 MHz) δ 9.06 (1H, s), 8.27 (2H, d, J=8.8 Hz), 7.61 (1H, s), 7.55 (2H, d, J=8.8 Hz), 5.63 (2H, s) and 3.81 (2H. s) ppm.

Step D: N-[2(S)-N'-(1-(4-Nitrophenylmethyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester bis trifluoroacetate

To a solution of 1-(4-nitrophenylmethyl)-1H-imidazol-5-ylacetic acid hydrochloride, N-[2(S)-amino-3(S)-methylpentyl]-N-naphthylmethyl-glycyl-methionine methyl ester bis hydrochloride (209 mg, 0.392 mmol) and 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOOBT, 64 mg, 0.39 mmol) in methylene chloride (10 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 75.2 mg, 0.392 mmol) and triethylamine (219 μl, 1.57 mmol) and the mixture stirred overnight at room temperature. After this time, satd. aq. sodium bicarbonate (10 ml) was added and the mixture was extracted with methylene chloride. The combined extracts were washed with satd. aq. sodium bicarbonate (10 ml) and the solvent evaporated *in vacuo.*

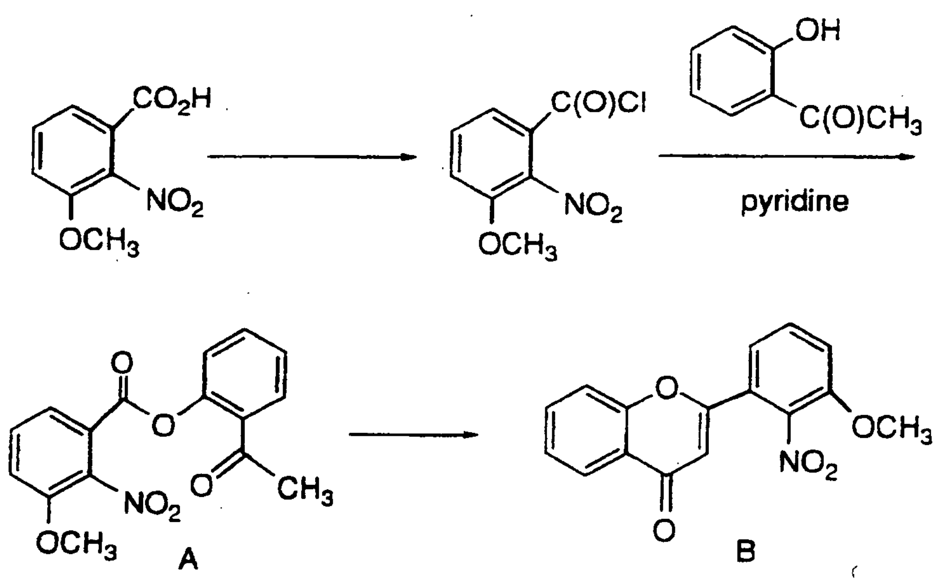
EXAMPLE 7

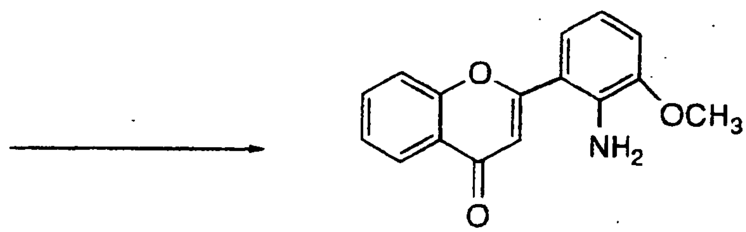
2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester



The title compound is prepared in accordance with WO 94/10138 published on May 11, 1994, incorporated by reference.

EXAMPLE 8
2-(2-AMINO-3-METHOXYPHENYL)
-1-BENZOPYRAN-4-ONE





2-nitro-3-methoxybenzoic acid (5.0 g, 0.0254 moles, 1 eq.) was combined with dichloromethane (50 mL) and dimethylformamide (0.1 mL) cooled to 0°c under nitrogen and oxalyl chloride (3.0 mL, 0.033 moles 1.3 eq) added. The reaction was allowed to stir at room temperature overnite and then concentrated to an oil. A solution of 2-hydroxyacetophenone (5.2 gm, 0.038 moles) in pyridine (5 mL) was added. After stirring (20 min) the mixture was poured into HCl in water (3%, 150 mL) and ice (50g), stirred for 30 min.and filtered. The filter cake was washed with H_2O (10 ml) , methanol (5 mL) and H_2O (5 mL).

The wet solid was resuspended in methanol (6 mL), warmed to reflux, cooled and filtered to give (4.6 g) of the nitro-substituted ester A.

Nitro ester A (2.5 g) was combined with pyridine (7 mL) warmed to 50°C and pulverized KOH (670 mg, 86%, 1.3 eq.) added. The mixture was stirred and solidified after 5 min. The mixture was acidified with acetic acid (10 mL) and filtered. The solid was the treated with acetic acid (9ml) and sulfuric acid (0.35ml) and was then heated to 100°C for 1 hour.

The reaction was cooled, poured into ice (50 gm), and extracted with ethyl acetate. The ethyl acetate extracts were dried over Na_2SO_4 and concentrated to produce the nitro-fluorone B as a solid (1.56 g).

To nitroflavone B (1.33 g) in acetic acid (60 mL) was added a solution of $TiCl_3$/HCl solution (22 ml). The mixture was stirred for 2 hrs at RT. The mixture was poured into H_2O/$NaHCO_3$/ethyl acetate. The organic layer was separated, washed with H_2O, dried over Na_2SO_4, filtered and concentrated

to a foam. The foam was chromatographed on silica using 40% ethyl acetate/hexanes to produce the title compound as a yellow foam (1.10 g).

BIOLOGICAL ASSAYS.

The ability of compounds of the present invention to inhibit cancer can be demonstrated using the following assays.

Raf kinase assay

Raf kinase activity *in vitro* is measured by the phosphorylation of its physiological substrate MEK (Map/ERK kinase). Phosphorylated MEK is subsequently trapped on a filter membrane and incorporation of radio-labeled phosphate is quantitated by scintillation counting.

MATERIALS

Activated Raf

Produced in Sf9 insect cells coinfected with three different baculoviruses expressing epitope-tagged Raf, and the upstream activators Val^{12}-H-Ras, and Lck. The epitope sequence Glu-Tyr-Met-Pro-Met-Glu ("Glu-Glu") was fused to the carboxy-terminus of full-length c-Raf.

MEK

Catalytically inactive MEK is produced in Sf9 cells infected with baculovirus expressing epitope-tagged MEK with a $lysine^{97}$ to alanine mutation (K97A). The epitope sequence Glu-Tyr-Met-Pro-Met-Glu ("Glu-Glu") was fused to the amino-terminus of full-length MEK1.

Anti "Glu-Glu" antibody

A hybridoma cell line expressing an antibody specific for the "Glu-Glu" epitope was obtained from Gernot Walter, UCSD. Cells were grown and antibodies were purified as described (Grussenmeyer et al., Proc. Natl. Acad. Sci. U.S.A., 82, pp. 7952-7954, 1985).

Column buffer

20 mM Tris, pH 8, 100 mM NaCl, 1 mM EDTA, 2.5 mM EGTA, 10 mM $MgCl_2$, 2 mM DTT, 0.4 mM AEBSF, 0.1% n-octyl glucopyranoside, 1 nM okadeic acid, and 10 μg/ml each of benzamidine, leupeptin, pepstatin, and aprotinin (all SIGMA).

5x reaction buffer

125 mM HEPES pH=8.0, 25 mM $MgCl_2$, 5 mM EDTA, 5 mM Na_3VO_4, 100 μg/ml BSA

Enzyme dilution buffer

25 mM HEPES pH=8.0, 1 mM EDTA, 1 mM Na_3VO_4, 400 μg/ml BSA.

Stop solution

100 mM EDTA, 80 mM sodium pyrophosphate.

Filter plates

Millipore Multiscreen #SE3M078E3, Immobilon-P (PVDF).

METHOD

A. Protein purification

1. Sf9 insect cells were infected with baculovirus and grown as described (Williams et al., Proc. Natl. Acad. Sci. U.S.A., 89, pp. 2922-2926, 1992).
2. All subsequent steps were performed on ice or at 4°C. Cells were pelleted and lysed by sonication in column buffer. Lysates were spun at 17,000x g for 20 min, followed by 0.22 μm filtration.
3. Epitope-tagged proteins were purified by chromatography over a GammaBind Plus (Pharmacia) affinity column to which "Glu-Glu" antibody had been coupled. Proteins were loaded on the column, followed by washes with two column volumes of column buffer, and eluted with 50 μg/ml of peptide antigen (Glu-Tyr-Met-Pro-Met-Glu) in column buffer.

B. Raf kinase assay

1. Add 10 µl of inhibitor or control in 10% DMSO to assay plate.
2. Add 30 µl of reaction mix containing 10 µl 5x reaction buffer and 0.5 µl 1mM ^{33}P-γ-ATP (20 µCi/ml), 0.5 µl MEK (2.5 mg/ml), 1 µl 50 mM β-mercaptoethanol.
3. Start reaction by addition of 10 µl enzyme dilution buffer containing 1 mM DTT and an empirically determined amount of activated Raf that produces linear incorporation kinetics over the reaction time course.
4. Mix and incubate at room temperature for 90 min.
5. Stop reaction by addition of 50 µl stop solution.
6. Prewet filter plate with 70% ethanol and rinse with water.
7. Transfer 90 µl aliquots of stopped reaction to filter plate.
8. Aspirate and wash four times with 200 µl H_2O.
9. Add 50 µl scintillation cocktail, seal plate, and count in Packard TopCount scintillation counter.

Map Kinase Phosphorylation assay

Inhibition of Raf kinase activity in intact cells is measured by determining the phosphorylation state of Map Kinase in TPA-stimulated C-33a human epithelial cells. Phosphorylated Map Kinase is detected by "Western" blot using an anti-phospho-Map Kinase antibody.

Materials

C33a Human Epithelial Cells

The C33a cell line is obtained from the ATCC repository, catalog # H TB31, and is maintained in DMEM (Mediatech) + 10 % fetal bovine serum +1% penicillin/streptomycin (Gibco) according to the instructions provided.

Anti-phospho-MAP Kinase antibody

The rabbit polyclonal anti-phospho-MAP kinase antibody is obtained from New England Biolabs (Beverly, MA)

Secondary antibody

The anti-rabbit antibody-alkaline phosphatase conjugate is obtained from New England Biolabs

Acrylamide Gel

Ten percent *bis*-acrylamide electrophoresis gels were obtained from Novex.

Blocking Buffer

1x Phosphate-buffered saline, 0.1 % Tween-20, 5 % nonfat dry milk.

Antibody dilution buffer

1x phosphate-buffered saline, 0.05 % Tween-20, 5 % bovine serum albumin

Alkaline phosphatase substrate

The chemiluminescent alkaline phosphatase substrate, CDP-Star™, is obtained from New England Biolabs.

Assay Buffer

0.1 M diethanolamine, 1 mM $MgCl_2$.

Method

1. C33a cells are grown to confluency in 24 well plates, then starved for 24 hr in DMEM + 0.5 % charcoal-stripped serum.

2. Compound to be tested, dissolved in DMSO at 1000x concentration, is added to each well.

3. One hour later, TPA (dissolved in DMSO at 1000x concentratrion) is added at a final concentration of 100 ng/ml.

4. Twenty minutes later, the media is removed from all wells, and 100 μl of boiling hot reducing Laemmli sample buffer is added to each well. The plate is agitated, and the cell lysate is transferred to a 1.5 ml plastic microcentrifuge tube. Each lysate is then sonicated for 10 s, and placed in a boiling water bath for 5-10 minutes. Fifteen microliters of each sample is then loaded on a 10% Laemmli polyacrylamide gel (Novex), and the gel electrophoresed according to the manufacturer's instructions.

5. Proteins in the gel are electroblotted to a PVDF membrane, which is then rinsed in PBS and blocked with Blocking Buffer for approximately 1 hr at room temperature.

6. The PVDF membrane is rinsed in PBS. The anti-phospho-MapK antibody, diluted approximately 1:500 in antibody dilution buffer, is incubated with the PVDF membrane with gentle agitation overnight at 4°C.

7. The PVDF membrane is rinsed 3 times for 5 minutes with Blocking Buffer, then incubated with the secondary antibody, diluted approximately 1 : 1000 in antibody dilution buffer, for 1 hr with gentle agitation at room temperature.

8. The PVDF membrane is rinsed 5 times for 5 minutes with Blocking Buffer, then incubated with the chemiluminescent alkaline phosphatase substrate dissolved in Assay Buffer for approximately 5 minutes. The membrane is then rinsed, wrapped in plastic, and exposed to x-ray film to detect blotted proteins.

In the Raf kinase inhibition assay, the IC_{50} ranges from about 0.001 μM to about 1.5 μM.

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase.

Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber et al., J. Biol. Chem. 265:14701-14704 (1990), Pompliano, et al., Biochemistry 31:3800 (1992) and Gibbs et al., PNAS U.S.A. 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 μl containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 100 mM [^{3}H]-farnesyl diphosphate ([^{3}H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 μg/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvestor, washed with 100% ethanol, dried and counted in an LKB β-plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^{3}H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer et al., Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 μM $ZnCl_2$ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 μl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The farnesyl protein transferase inhibiting compounds are tested for inhibitory activity against human FPTase by the assay described above and the compounds can generally be found to have IC_{50} of approximately 50 μM.

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemeted with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[^{35}S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM $MgCl_2$/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

In vivo growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-*ras*, v-*raf*, or v-*mos* oncogene is tested. Cells transformed by v-Raf

and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1 x 10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

Protocol for MEK Protein Kinase-MEKKA

I. INTRODUCTION

MAP kinase (mitogen-activated protein kinase) or ERK (extracellular signal regulated kinase) plays an important role in the growth factor signal transduction. ERK is activated by both tyrosine and threonine phosphorylation upon growth factor stimulation. The phosphorylation is mediated by a protein kinase which is known as MAP kinase kinase or MEK(MAP kinase or ERK kinase). MEK1 and MEK2 encode 393 and 400 amino acids respectively. Both proteins are similar and stimulate threonine and tyrosine phosphorylation on ERK.

II. EQUIPMENT AND SUPPLIES

Costar round bottom polypropylene plates (#3974)
Magnetic plate stirrer
Millipore 0.45 uM Immobilon-P Membrane (Millipore MAIPNOB50)
Packard Multiscreen Adaptor (#PPN6005178)
Packard Plate Sealer

Packard Top Count
pH Meter
12 or 8-channel pipette
Repeater pipette
TOMTEC Quadra 96 pipettor
TomTech Filtration unit
Top Seal-S (Packard #6005161)
Transtar-96 (Costar #7605)
Transtar-96 Cartridges (Costar #7606)
Transtar-96 Elevator (Costar #7610)

III. REAGENTS

Adenosine 5'-Triphosphate (Pharmacia #27-1006-01)
^{33}[P]-γ-ATP (NEN #602H)/^{32}[P]-γ-ATP (Amersham #AA0018)
Bovine Serum Albumin (Sigma #A-7030)
EDTA (Sigma #60-00-4)
HEPES (Sigma #H-3375)
Magnesium Chloride (Fluka #63064)
MEK Enzyme (Merck-West Point)
β-Mercaptoethanol (Sigma #M-3148)
GST-MAPK Substrate(Merck-West Point)
Sodium Hydroxide pellets (Sigma #0899)
Sodium Orthovanadate (Sigma #S6508)
Sodium Pyrophosphate (Sigma #13472-36-1)
Tris (Sigma #77-86-1)

IV. PREPARATION BEFORE ASSAY

A. Buffers/Reagents:

1. ASSAY BUFFER (10x) - (Final assay Conc. 50mM HEPES, 15mM $MgCl_2$, 100ug/ml BSA, 400uM Sodium Orthovanadate, 1mM EDTA pH 8.0)

a. Dissolve 119.15g HEPES (MW 238.3), 30.4965g Magnesium Chloride (MW 203.31) 1g BSA, 0.7356g Sodium Orthovanadate (MW 183.9), 2.922g EDTA (MW 292.2) in 800 ml of water, adjust pH to 8.0 and adjust volume to 1000 ml

b. Aliquot and store at -20°C

2. ENZYME BUFFER (10X) - (Final assay Conc. 25mM HEPES, 200ug/ml BSA, 200uM Sodium Orthovanadate, 500uM EDTA pH 8.0)

a. Dissolve 59.575g HEPES (MW 238.3), 2g BSA, 0.3678g Sodium Orthovanadate (MW 183.9), 1.461g EDTA (MW 292.2) in 800ml of water, adjust pH to 8.0 and adjust volume to 1000ml.

b. Aliquot and store at -20°C.

3. Cold ATP - 10mM (Final conc 10μM)

a. Dissolve 0.06052g of Adenosine 5'-Triphosphate (MW 605.2) in 10ml water.

b. Aliquot and store at -20°C.

4. Staurosporine MW466.5 (IC50 ~ 1nM)

a. Dissolve in DMSO for storage.

b. Further dilute in 50% DMSO as needed.

5. 1M EDTA MW 292.2

a. Dissolve 292.2g in 700ml of water, increase pH with NaOH pellets

b. Neutralize EDTA solution

6. 1L STOP SOLUTION 250mM EDTA, 250mM Sodium Pyrophosphate (Final assay conc. 125mM EDTA, 125mM Sodium Pyrophosphate)

a. Add 111.525g of Sodium Pyrophosphate (MW 446.1) to 500ml water in 1-2L beaker.

b. Add 250ml of 1M EDTA solution (see above step 5)

c. Stir until all dissolved (addition of heat necessary to dissolve Sodium Pyrophosphate).

d. Bring level of solution to 1L.

7. β-Mercaptoethanol (Final Conc. 2.38mM)

a. Dilute 1:100 of 14.3M solution in water.

b. Prepare fresh before assay.

8. 20mM Tris Buffer pH 8.0

a. Add 2.4228g Tris (MW 121.14) to 800ml water.

b. Adjust pH to 8.0, adjust volume to 1000ml.

V. ASSAY PROCEDURES

A. Sample Preparation

1. Resuspend MEK extracted samples in 100% DMSO and dilute with 50% aqueous DMSO for a final assay concentration of 5 to 20 µl wbe/ml (to be piloted at CIBE). The final solvent concentration should be 2.5% DMSO.

2. The C-18 extracts are dissolved in 75% aqueous DMSO and then diluted with 50% aqueous DMSO.

B. Reagent Preparation

1. MAPK MIX - Total Volume 40µl/well - See table below, scale up as needed, keep all reagents on ice until use

MAPK MIX	40µl/well
10X Buffer	3.333
water	35.501
B-ME 142mM	0.833
MAP (1:300)	0.333

Order of addition is important: Water, buffer, β-Mercaptoethanol, then GST-MAPK Protein Substrate should be added last.

*Note: Volume of GST-MAPK Protein Substrate subject to change from batch to batch, please adjust volume of water when necessary

2. MEK/ATP MIX - (^{33}[P]-γ-ATP - final conc 20uCi/ml/Cold ATP - final conc 10uM in assay) - Total Volume 20µl/well

a. Store ^{33}[P]-γ-ATP (easy tides) or ^{32}[P]-γ-ATP (redivue) at 4°C.

b. See Table below for recipe, scale up as needed, keep on ice until use

MEK/ATP MIX	20µl/well
Enz Dil Buffer	3.333
water	15.251
B-ME 142mM	0.833
10mM Cold ATP (10uM)	0.1
Hot ATP	0.15
Activated MEK (PHJ-1Prep1:300)	0.333

Order of addition is important: Water, buffer, β-Mercaptoethanol, cold ATP, Hot ATP, and then enzyme should be added last.

* Note: Amount of Hot ATP is subject to change. Volume of MEK Enzyme subject to change from batch to batch, please adjust volume of water when necessary

C. Assay Steps

1. Add with Quadra 96 to round bottom polyproylene plate: 35µl water + 5µl DMSO sample or pos control (50mM EDTA Final) or IC_{50} (Staurosporine). Both positive control (in triplicate) and IC_{50} should be run for each plate.

2. Add 40µl of MAP mix per well with 8 or 12-channel pipette

3. Add 20µl of MEK/ATP dilution per well with 8 or 12-channel pipette

4. Incubate at room temp. for 2hr

5. Add 100µl of stop solution

6. Pre-wet filter plate with 100µl Methanol

7. Wash filter plate 3X with 100µl water per well

8. Transfer 175ul liquid from polypropylene plate to filter plate with the Transtar 96 pipettor (remember to change cartridges after each plate)

9. Filter wells using the TomTec filtration unit - stop vacuum

10. Wash plate 5 times with 300µl of 20mM Tris buffer pH 8.0 per well (stop vacuum after each filtration) with Quadra 96 in dry mode.

11. Peel off bottom of filter, blot bottom of plate dry with paper towels

12. Place plate adaptor on filter plate

D. Counting Procedure

1. Add 50µl of Microscint-20 scintillation fluid with repeater pipette

2. Seal plate with plate sealer - use Packard Top Seal-S

3. Place plate in Top Count.

VI. CALCULATION

$$\% \text{ INHIBITION} = \frac{\text{(CPMavg total binding) - (CPMsample)}}{\text{(CPMavg total binding) - (CPMavg positive control)}} \times 100$$

When the broth extract shows more than 65% and dose-related inhibition in MEKKA with low activity in both RAFKA and CyDKIK E2 the broth is considered an interesting active for further study at Rahway and West Point..

VIII. REFERENCES

1. Crews et al., Science **258**, 478-480, 1992.

2. Zheng and Guan, J. Biol Chem. **268**,11435-11439, 1993.

3. Wu et al., Proc. Natl. Acad. Sci. USA **90**, 173-177, 1993.

4. Cowley et al., Cell **77**, 841-852, 1994.

WHAT IS CLAIMED IS:

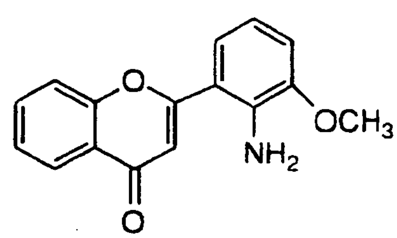
1. A method of treating cancer comprising admininstering to a mammalian patient in need of such treatment an effective amount of a MEK inhibiting compound and an effective amount of a farnesyl protein transferase inhibiting compound.

2. A method of treating cancer in accordance with claim 1 wherein the cancer is selected from the group consisting of: cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung.

3. A method of treating cancer in accordance with claim 1 wherein the cancer is selected from the group consisting of: histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers.

4. A method of treating cancer in accordance with claim 1 wherein the cancer is selected from the group consisting of: pancreatic and breast carcinoma.

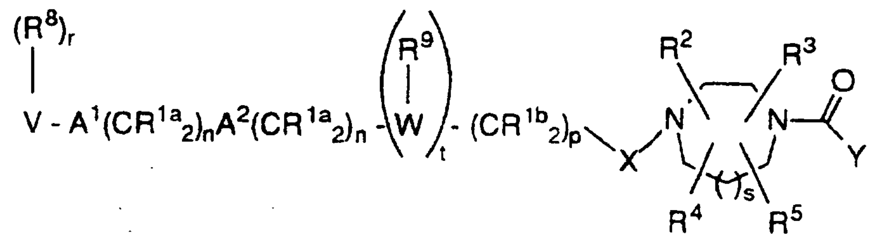
5. A method of treating cancer in accordance with claim 1 wherein the MEK inhibiting compound is selected from the group consisting of:



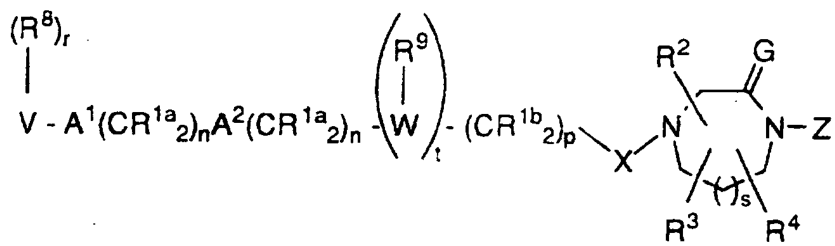
or a pharmaceutically acceptable salt thereof.

6. A method of treating cancer in accordance with claim 1 wherein the farnesyl transferase inhibiting compound is selected from the group consisting of:

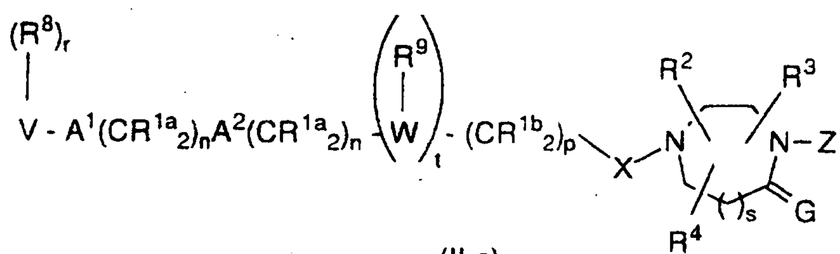
(a) a compound represented by one of formulas (II-a) through (II-c):



(II-a)

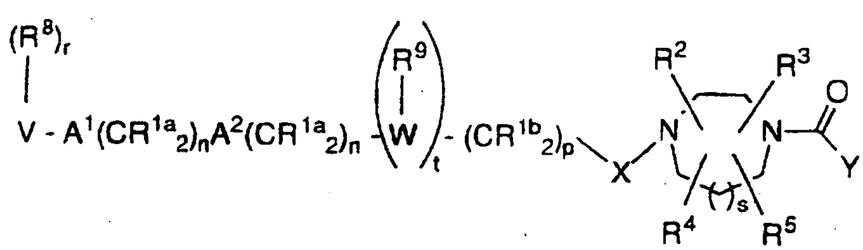


(II-b)



(II-c)

or a pharmaceuticaly acceptable salt thereof, wherein with respect to formula (II-a):



(II-a)

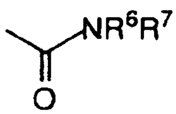
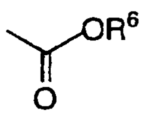
R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

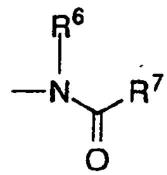
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

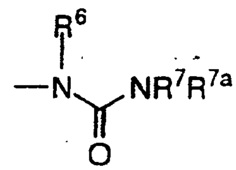

or

,

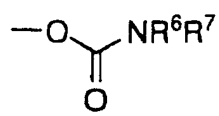
wherein the substituted group is substituted with one or more of:

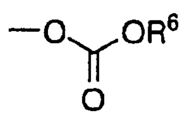
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^6, $S(O)R^6$, SO_2R^6,

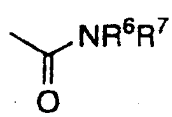
5) $-NR^6R^7$,

6)  ,

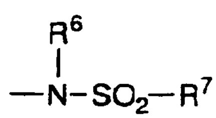
7)  ,

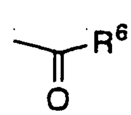
8)  ,

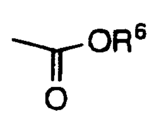
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  , or

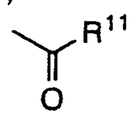
14)  ; or

R^2 and R^3 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and $-N(COR^{10})-$;

R^4 and R^5 are independently selected from H and CH_3;

and any two of R^2, R^3, R^4 and R^5 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $—SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-$C(NH)$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

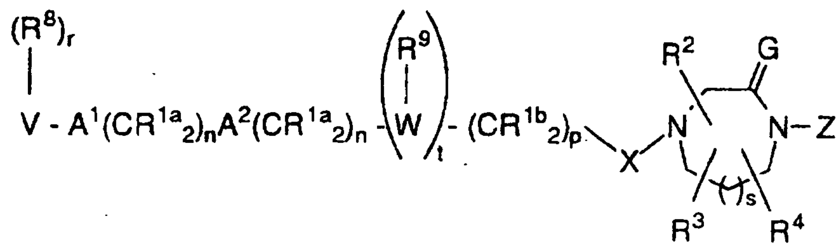
X is $-CH_2-$, $-C(=O)-$, or $-S(=O)_m-$;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1; and
u is 4 or 5;

with respect to formula (II-b):



(II-b)

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, R^{7a}, u, R^8, A^1, A^2, V, W, X, n, p, r, s, t and u are as defined above with respect to formula (II-a);

R^4 is selected from H and CH_3;

and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^9 is selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

G is H_2 or O;

Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

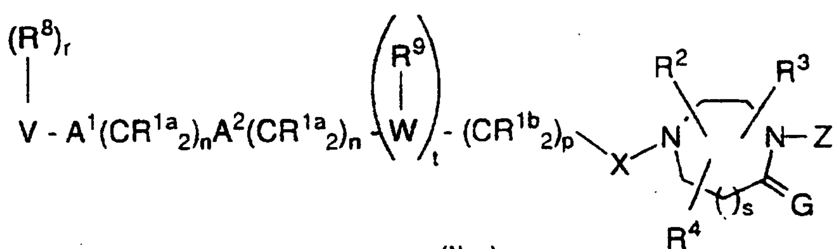
1) C_{1-4} alkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) aryl or heterocycle,
e) HO,
f) $-S(O)_mR^6$, or
g) $-C(O)NR^6R^7$,

2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

with respect to formula (II-c):



(II-c)

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, u, R^{7a}, R^8, A^1, A^2, V, W, X, n, r and t are as defined above with respect to formula (II-a);

R^4 is selected from H and CH_3;

and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

G is O;

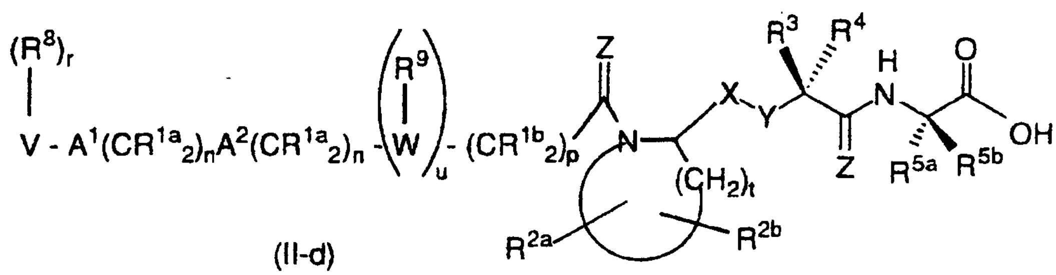
Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

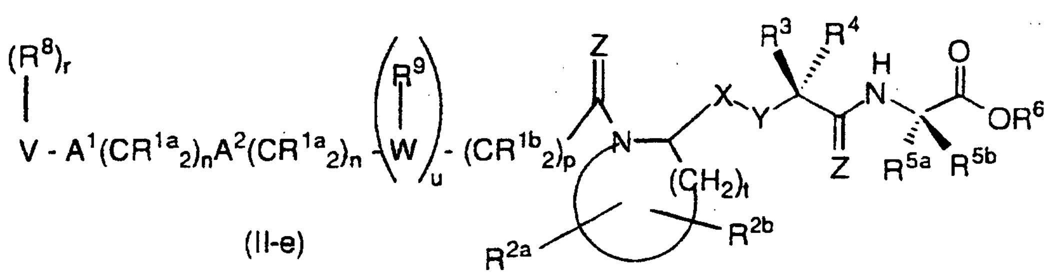
and

s is 1;

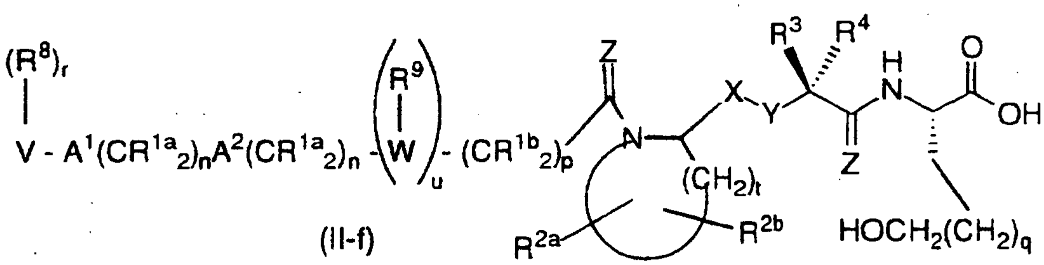
(b) a compound represented by formula (II-d) through (II-g):



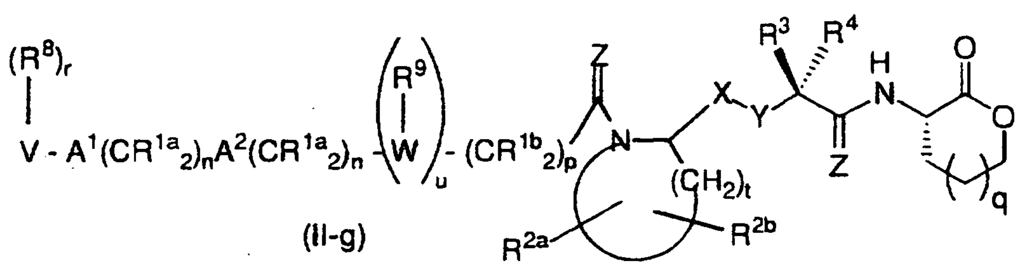
(II-d)



(II-e)

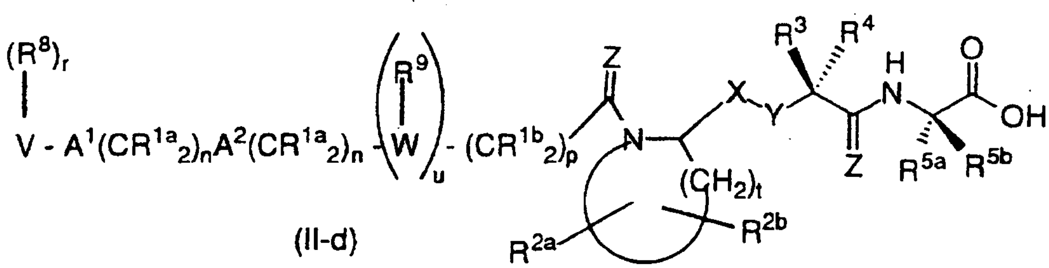


(II-f)



(II-g)

wherein with respect to formula (II-d):



(II-d)

R^{11}, V, W, m, n, p and r are as defined above with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^{2a} and R^{2b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from:

a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone, and
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,
   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^3 and R^4 are combined to form - $(CH_2)_s$ - ;

R^{5a} and R^{5b} are independently selected from:

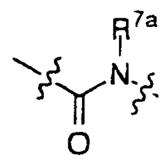
a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone,
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,
   wherein the substituent is selected from F, Cl, Br, CF_3, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-,

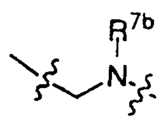
$R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl,

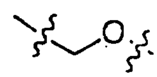
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

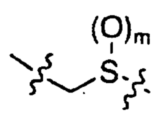
R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and $-N(COR^{10})$- ;

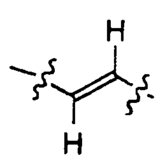
X-Y is

a)  ,

b)  ,

c)  ,

d)  ,

e)  , or

f) $-CH_2-CH_2-$;

R^{7a} is selected from

a) hydrogen,

b) unsubstituted or substituted aryl,

c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^{7b} is selected from
a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl,
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl,
f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl, and
g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^8 is independently selected from:
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6

alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-C(NH)-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

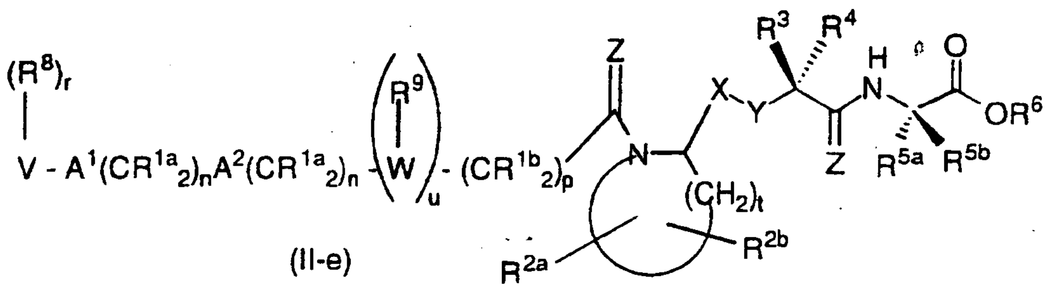
R^{10} is independently selected from H, C_1-C_6 alkyl, benzyl, substituted aryl and C_1-C_6 alkyl substituted with substituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

Z is independently H_2 or O;

s is 4 or 5;
t is 3, 4 or 5; and
u is 0 or 1;

with respect to formula (II-e):



(II-e)

R^{11}, W, m, n, p and r are as defined above with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^{2a} and R^{2b} are independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from:

a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone,
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,
   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^3 and R^4 are combined to form - $(CH_2)_s$ - ;

R^{5a} and R^{5b} are independently selected from:

a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone,
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,
   wherein the substituent is selected from F, Cl, Br, CF_3, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-,

$R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

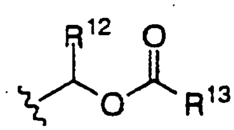
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and $-N(COR^{10})$- ;

R^6 is

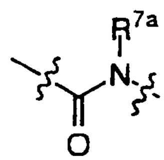
a) substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_5-C_8 cycloalkyl, or substituted or unsubstituted cyclic amine, wherein the substituted alkyl, cycloalkyl or cyclic amine is substituted with 1 or 2 substituents independently selected from:
1) C_1-C_6 alkyl,
2) aryl,
3) heterocycle,
4) $-N(R^{11})_2$,
5) $-OR^{10}$, or

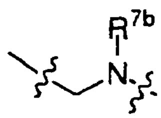
b)

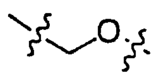


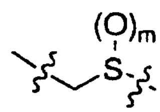
;

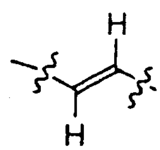
X-Y is

a)  ,

b)  ,

c)  ,

d)  ,

e)  , or

f) $-CH_2-CH_2-$;

R7a is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R7b is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,.
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl,

e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl,

f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl, and

g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-$C(NH)$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from H, C_1-C_6 alkyl, benzyl, substituted aryl and C_1-C_6 alkyl substituted with substituted aryl;

R^{12} is hydrogen or C_1-C_6 alkyl;

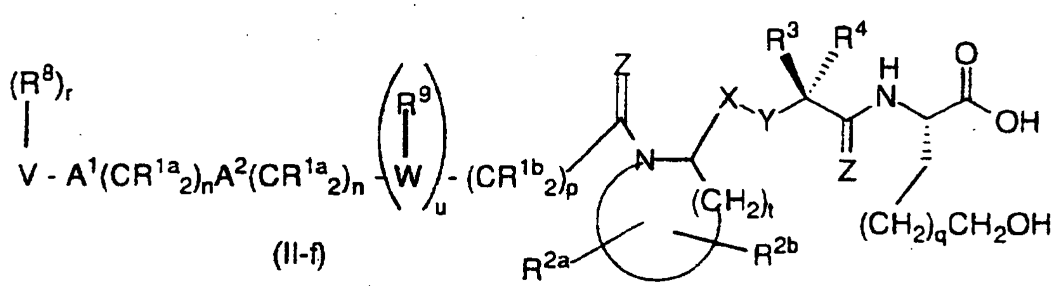
R^{13} is C_1-C_6 alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^{10}$-, $-NR^{10}C(O)$-, O, $-N(R^{10})$-, $-S(O)_2N(R^{10})$-, $-N(R^{10})S(O)_2$-, or $S(O)_m$;

Z is independently H_2 or O;

s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

with respect to formula (II-f):



(II-f)

R^{11}, V, W, m, n, p and r are as defined above with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^{2a} and R^{2b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

   i) methionine sulfoxide, or

   ii) methionine sulfone, and

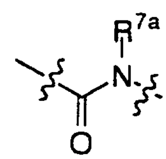
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

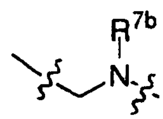
wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

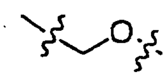
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

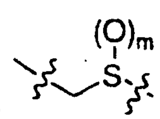
R^3 and R^4 are combined to form - $(CH_2)_s$ - ;

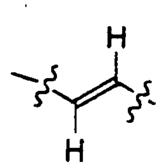
X-Y is

a)  ,

b)  ,

c)  ,

d)  ,

e)  , or

f) -CH_2-CH_2- ;

R^{7a} is selected from

a) hydrogen,

b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^{7b} is selected from
a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl,
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl,
f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl, and
g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^8 is independently selected from:
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-C(NH)-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from H, C_1-C_6 alkyl, benzyl, substituted aryl and C_1-C_6 alkyl substituted with substituted aryl;

R^{12} is hydrogen or C_1-C_6 alkyl;

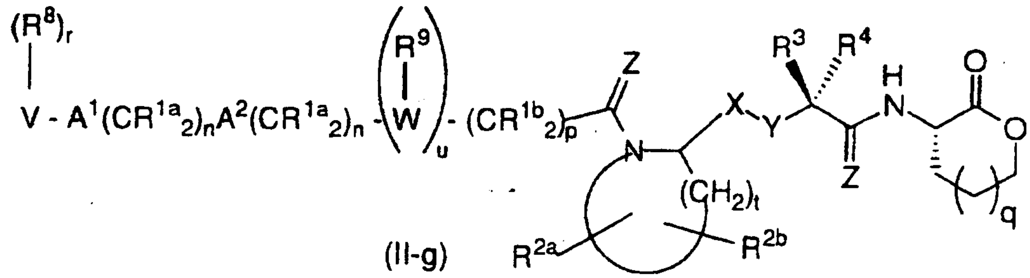
R^{13} is C_1-C_6 alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

Z is independently H_2 or O;

q is	0, 1 or 2;
s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

with respect to formula (II-g):



(II-g)

R^{11}, V, W, m, n, p and r are as previously defined with respect to formula (II-a);

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN. NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

R^{2a} and R^{2b} are independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl unsubstituted or substituted by C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2,

$(R^{10})_2N\text{-}C(NR^{10})\text{-}$, $R^{10}C(O)\text{-}$, $R^{10}OC(O)\text{-}$, N_3, $\text{-}N(R^{10})_2$ or $R^{11}OC(O)NR^{10}\text{-}$, and

d) $C_1\text{-}C_6$ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and $C_3\text{-}C_{10}$ cycloalkyl;

R^3 and R^4 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

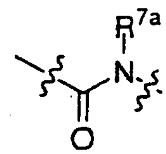
c) substituted or unsubstituted $C_1\text{-}C_{20}$ alkyl, $C_2\text{-}C_{20}$ alkenyl, $C_3\text{-}C_{10}$ cycloalkyl, aryl or heterocycle group,

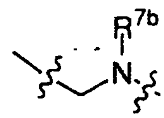
wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O\text{-}$, $R^{11}S(O)_m\text{-}$, $R^{10}C(O)NR^{10}\text{-}$, CN, $(R^{10})_2N\text{-}C(NR^{10})\text{-}$, $R^{10}C(O)\text{-}$, $R^{10}OC(O)\text{-}$, N_3, $\text{-}N(R^{10})_2$, $R^{11}OC(O)NR^{10}\text{-}$ and $C_1\text{-}C_{20}$ alkyl, and

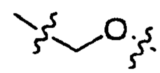
d) $C_1\text{-}C_6$ alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and $C_3\text{-}C_{10}$ cycloalkyl; or

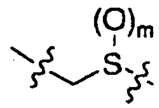
R^3 and R^4 are combined to form $\text{-}(CH_2)_s\text{-}$;

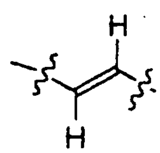
X-Y is

a)  ,

b)  ,

c)  ,

d)  ,

e)  , or

f) $-CH_2-CH_2-$;

R^{7a} is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^{7b} is selected from

a) hydrogen,
b) unsubstituted or substituted aryl,
c) unsubstituted or substituted heterocycle,

d) unsubstituted or substituted C_3-C_{10} cycloalkyl,

e) C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl,

f) a carbonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl, and

g) a sulfonyl group which is bonded to an unsubstituted or substituted group selected from aryl, heterocycle, C_3-C_{10} cycloalkyl and C_1-C_6 alkyl substituted with hydrogen or an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-$C(NH)$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from H, C_1-C_6 alkyl, benzyl, substituted aryl and C_1-C_6 alkyl substituted with substituted aryl;

R^{12} is hydrogen or C_1-C_6 alkyl;

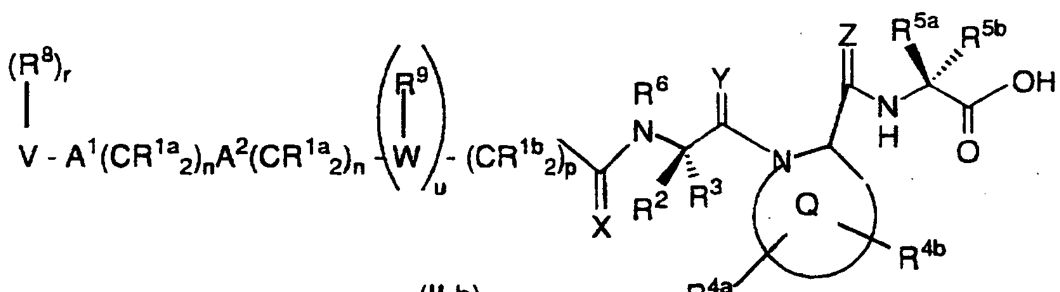
R^{13} is C_1-C_6 alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

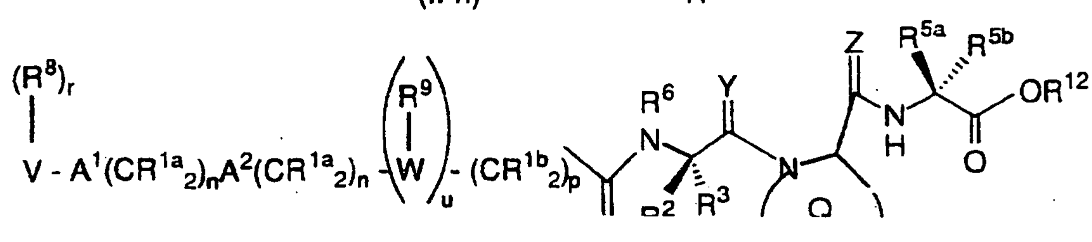
Z is independently H_2 or O;

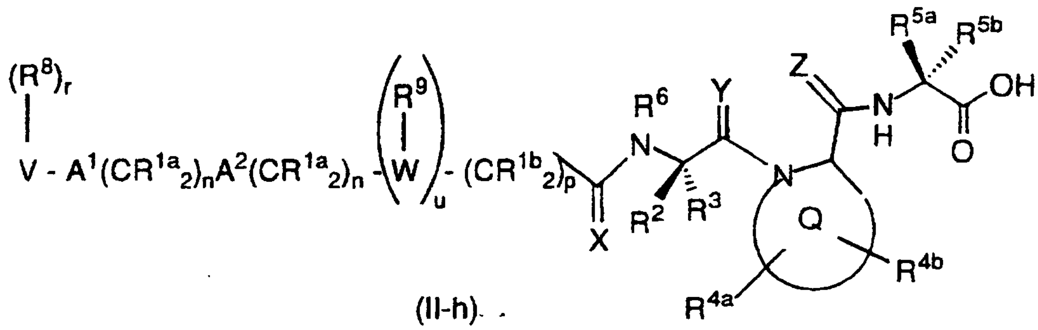
q is	0, 1 or 2;
s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

(c) a compound represented by one of formulas (II-h) through (II-k):



(II-h)





(II-h).

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as previously defined with respect to formula (II-a);

R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

  i) methionine sulfoxide, or

  ii) methionine sulfone, and

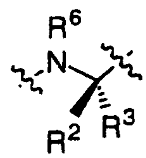
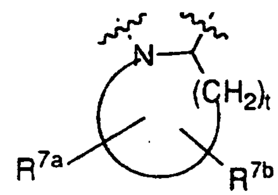
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

  wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form $-(CH_2)_s-$; or

R^2 or R^3 are combined with R^6 to form a ring such that

 is  ;

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^{5a} and R^{5b} are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or
   ii) methionine sulfone,

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,
   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl,

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and $-N(COR^{10})-$;

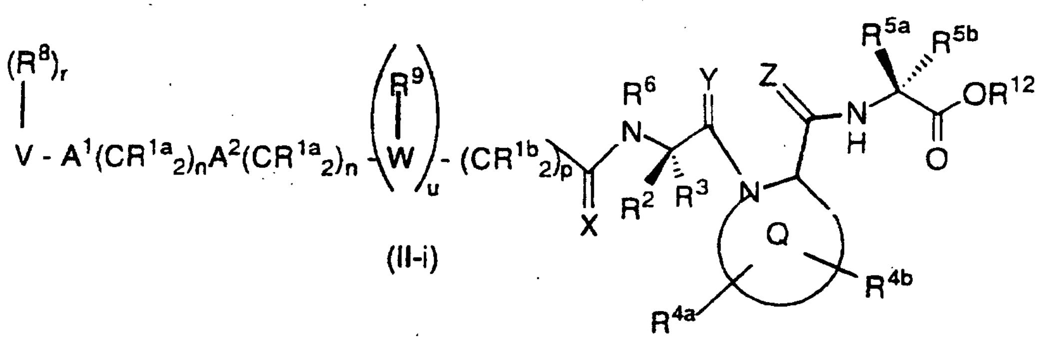
R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

with respect to formula (II-i):



(II-i)

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as previously defined with respect to formula (II-a);

R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,
b) an oxidized form of a side chain of a naturally occurring amino acid which is:
   i) methionine sulfoxide, or

ii) methionine sulfone, and

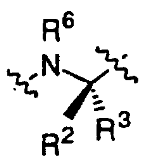
c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

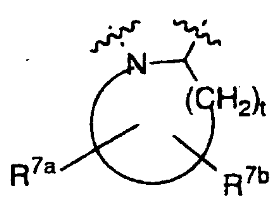
d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form - $(CH_2)_s$ - ; or

R^2 or R^3 are combined with R^6 to form a ring such that



is



;

R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

R^{5a} and R^{5b} are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

ii) methionine sulfone,

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocycle group,

wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl,

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^{5a} and R^{5b} are combined to form $-(CH_2)_s-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and $-N(COR^{10})$- ;

R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

R^{12} is

a) substituted or unsubstituted C_1-C_8 alkyl or substituted or unsubstituted C_5-C_8 cycloalkyl, wherein the substituent on the alkyl or cycloalkyl is selected from:

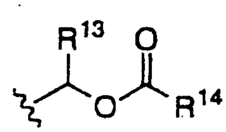
1) aryl,

2) heterocycle,

3) $-N(R^{11})_2$,

4) $-OR^{10}$, or

b)



;

R^{13} is independently selected from hydrogen and C_1-C_6 alkyl;

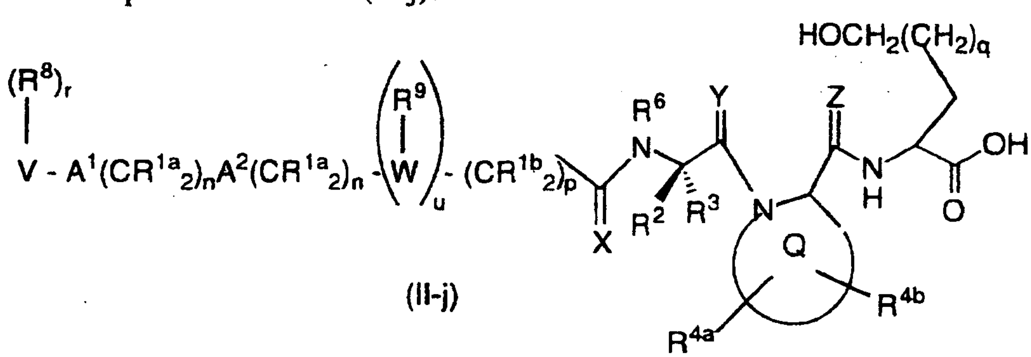
R^{14} is independently selected from C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

with respect to formula (II-j):



(II-j)

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p and r are as previously defined with respect to formula (II-a);

R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

i) methionine sulfoxide, or

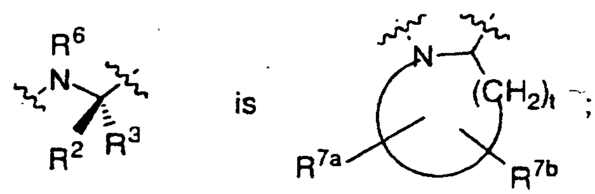
ii) methionine sulfone, and

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,
wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form - $(CH_2)_s$ - ; or

R^2 or R^3 are combined with R^6 to form a ring such that



R^{4a}, R^{4b}, R^{7a} and R^{7b} are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$- $C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

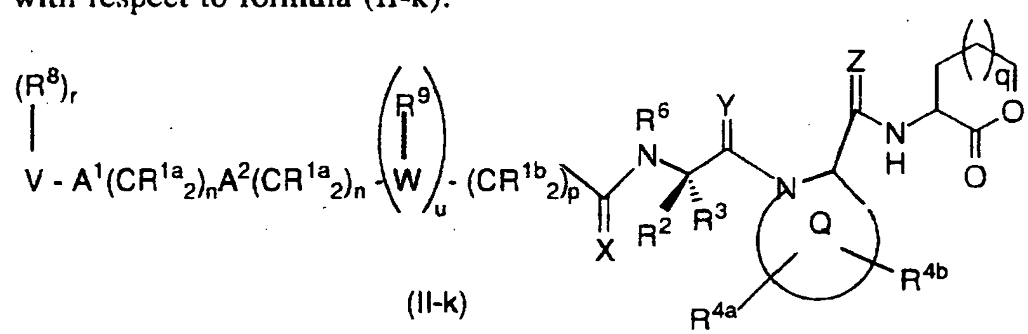
R^6 is independently selected from hydrogen or C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

q is	0, 1 or 2;
s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1;

with respect to formula (II-k):



(II-k)

R^{1a}, R^{1b}, R^8, R^9, R^{10}, R^{11}, A^1, A^2, V, W, m, n, p, and r are as defined above with respect to formula (II-a);

R^2 and R^3 are independently selected from:

a) a side chain of a naturally occurring amino acid,

b) an oxidized form of a side chain of a naturally occurring amino acid which is:

   i) methionine sulfoxide, or

   ii) methionine sulfone, and

c) substituted or unsubstituted C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{10} cycloalkyl, aryl or heterocyclyl group,

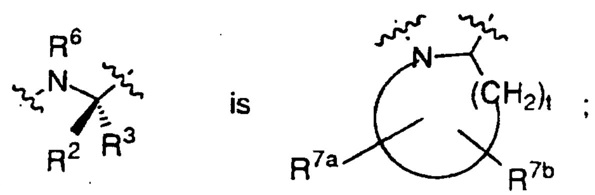
   wherein the substituent is selected from F, Cl, Br, $N(R^{10})_2$, NO_2, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-,

CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, $R^{11}OC(O)NR^{10}$- and C_1-C_{20} alkyl, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocycle and C_3-C_{10} cycloalkyl; or

R^2 and R^3 are combined to form - $(CH_2)_s$ - ; or

R^2 or R^3 are combined with R^6 to form a ring such that



R4a, R4b, R7a and R7b are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl unsubstituted or substituted by alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, N_3, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$ or $R^{11}OC(O)NR^{10}$-, and

d) C_1-C_6 alkyl substituted with an unsubstituted or substituted group selected from aryl, heterocyclyl and C_3-C_{10} cycloalkyl;

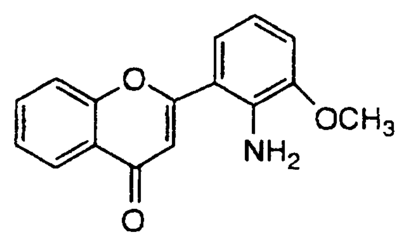
R6 is independently selected from hydrogen or C_1-C_6 alkyl;

Q is a substituted or unsubstituted nitrogen-containing C_4-C_9 mono or bicyclic ring system, wherein the non-nitrogen containing ring may be an aromatic ring, a C_5-C_7 saturated ring or a heterocycle;

X, Y and Z are independently H_2 or O;

q is	0, 1 or 2;
s is	4 or 5;
t is	3, 4 or 5; and
u is	0 or 1.

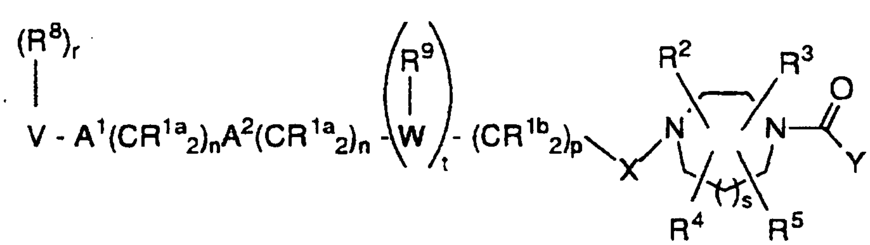
7. A method of treating cancer in accordance with claim 5 wherein the MEK inhibiting compound is:



or a pharmaceutically acceptable salt thereof.

8. A method of treating cancer in accordance with claim 6 wherein the farnesyl transferase inhibiting compound is

(a) a compound represented by one of formulas (II-a) through (II-c):



(II-a)

1-(2-amino-3-(2-benzyloxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2-amino-3-(2-hydroxyphenyl)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-[3-(4-imidazolyl)propyl]-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-*n*-butyl-4-(2,3-dimethylphenyl)-1-(4-imidazolylmethyl)-piperazin-5-one;

2(S)-*n*-butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;

1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)-2(S)-(2-methoxyethyl)piperazin-5-one;

2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(1-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(2-naphthylmethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-butyl-1-[1-(4-methoxybenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-butyl-1-[1-(3-methyl-2-butenyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-butyl-1-[1-(4-fluorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

2(S)-*n*-butyl-1-[1-(4-chlorobenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)piperazine;

1-[1-(4-bromobenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethylbenzyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-butyl-1-[1-(4-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

2(S)-*n*-butyl-1-[1-(3-methylbenzyl)imidazol-5-ylmethyl]-4-(1-naphthoyl)-piperazine;

1-[1-(4-phenylbenzyl)imidazol-5-ylmethyl]-2(S)-*n*-butyl-4-(1-naphthoyl)-piperazine;

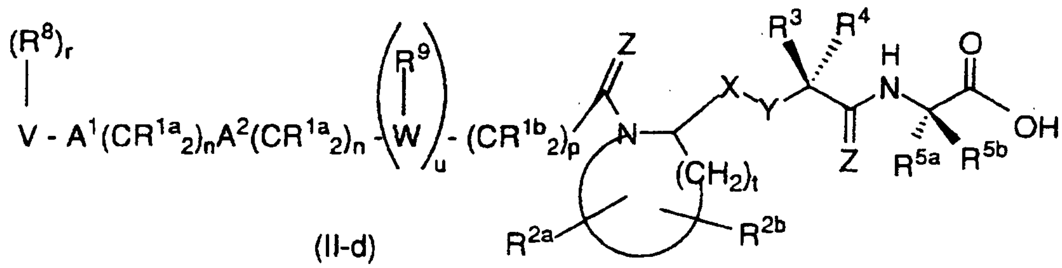
2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(2-phenylethyl)imidazol-5-ylmethyl]-piperazine;

2(S)-*n*-butyl-4-(1-naphthoyl)-1-[1-(4-trifluoromethoxy)imidazol-5-ylmethyl]piperazine;

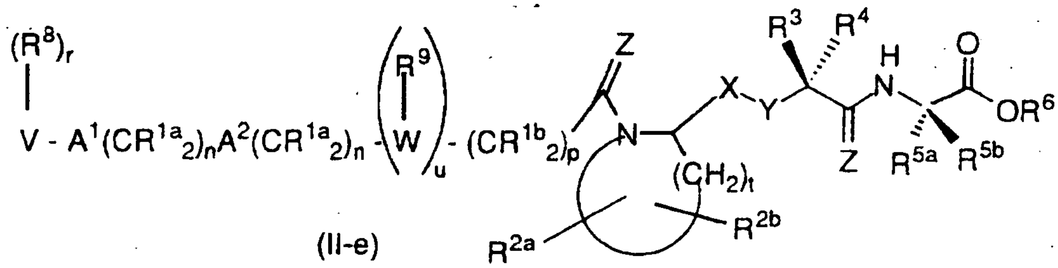
1-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetyl}-2(S)-*n*-butyl-4-(1-naphthoyl)piperazine;

or a pharmaceutically acceptable salt thereof.

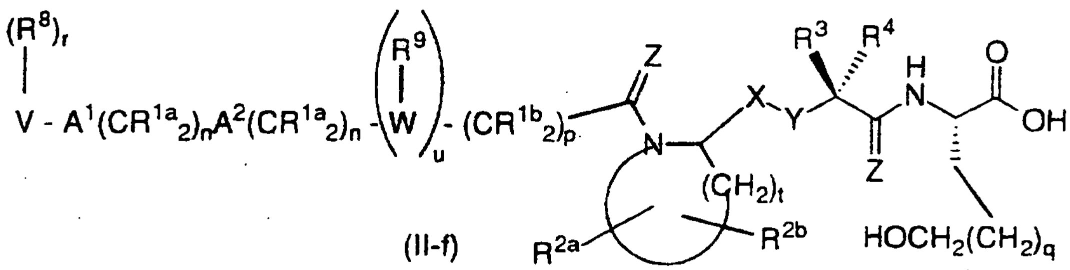
9. A method of treating cancer in accordance with claim 6 wherein the farnesyl transferase inhibiting compound is (b) a compound represented by one of formulas (II-d) through (II-g):



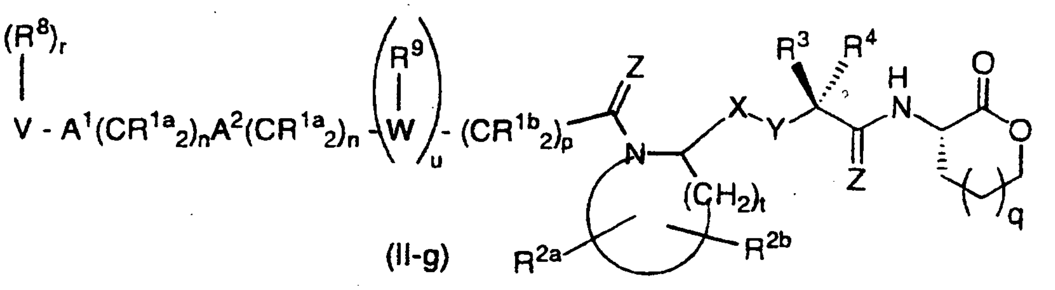
(II-d)



(II-e)



(II-f)



(II-g)

selected from the group consisting of:

N-[1-(4-imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycylmethionine

N-[1-(4-imidazoleacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2(S),3-diaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2(S),3-diaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(3-aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2(S)-amino-3-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2(S)-amino-3-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(3-amino-2(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-amino-2(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-glutaminyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(L-glutaminyl)pyrrolidin-2(S)- ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ;

N-[1-(L-histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(D-histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(D-histidyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(L-pyroglutamyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine isopropyl ester;

2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine sulfone;

2(S)-[1-(2(S)-pyroglutamyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine sulfone methyl ester;

2(S)-[1-(pyrid-3-ylcarboxy)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(S)-[1-(pyrid-3-ylcarboxy)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

2(R)-{2-[1-(naphth-2-yl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenylpropionyl-methionine;

2(R)-{2-[1-(naphth-2-yl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenylpropionyl-methionine methyl ester;

2(S)-[1-(pyrid-3-ylmethyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(S)-[1-(pyrid-3-ylmethyl)pyrrolidin-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine sulfone isopropyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine sulfone;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone methyl ester ;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine sulfone;

N-[1-(sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(N,N-dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

N-[1-(N,N-dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-acetylamino-3(S)-benzyloxycarbonylaminopropionyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-acetylamino-3(S)-aminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

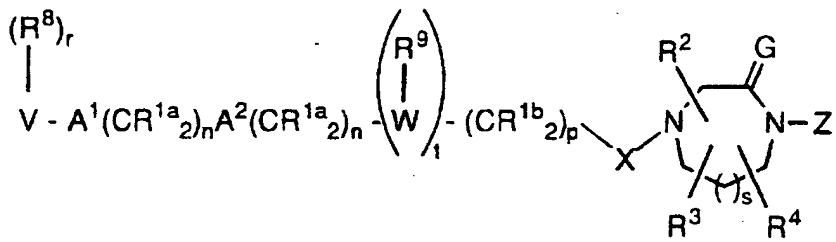
N-[1-(2-amino-3(S)-acetylaminopropionyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine methyl ester;

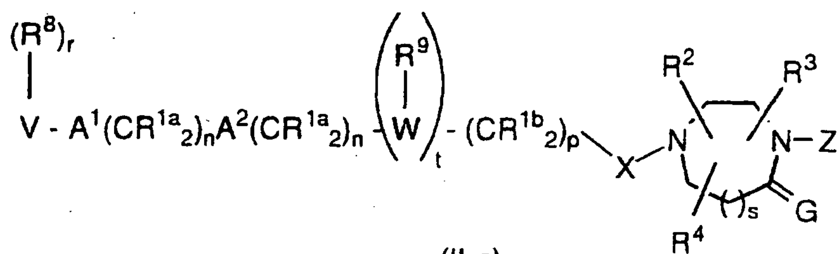
2(S)-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyloxy]-3-phenylpropionyl-methionine;

2(R)-{2-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester ;

2(R)-{2-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;



(II-b)



(II-c)

selected from the group consisting of:

2(S)-butyl-1-(2,3-diaminoprop-1-yl)-1-(1-naphthoyl)piperazine;

1-(3-amino-2-(2-naphthylmethylamino)prop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-{5-[1-(2-naphthylmethyl)]-4,5-dihydroimidazol}methyl-4-(1-naphthoyl)piperazine;

1-[5-(1-benzylimidazol)methyl]-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-{5-[1-(4-nitrobenzyl)]imidazolylmethyl}-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(3-acetamidomethylthio-2(R)-aminoprop-1-yl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-[2-(1-imidazolyl)ethyl]sulfonyl-4-(1-naphthoyl)piperazine;

2(R)-butyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

2(S)-butyl-4-(1-naphthoyl)-1-(3-pyridylmethyl)piperazine;

1-2(S)-butyl-(2(R)-(4-nitrobenzyl)amino-3-hydroxypropyl)-4-(1-naphthoyl)piperazine;

1-(2(R)-amino-3-hydroxyheptadecyl)-2(S)-butyl-4-(1-naphthoyl)-piperazine;

2(S)-benzyl-1-imidazolyl-4-methyl-4-(1-naphthoyl)piperazine;

1-(2(R)-amino-3-(3-benzylthio)propyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-amino-3-[3-(4-nitrobenzylthio)propyl])-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-[(4-imidazolyl)ethyl]-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-[(4-imidazolyl)methyl]-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)acetyl]-4-(1-naphthoyl)piperazine;

2(S)-butyl-1-[(1-naphth-2-ylmethyl)-1H-imidazol-5-yl)ethyl]-4-(1-naphthoyl)piperazine;

1-(2(R)-amino-3-hydroypropyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

1-(2(R)-amino-4-hydroxybutyl)-2(S)-butyl-4-(1-naphthoyl)piperazine;

2(R)-{2-[1-(4-nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;

2(R)-{2-[1-(4-nitrobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

2(R)-{2-[1-(4-methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;

2(R)-{2-[1-(4-methoxybenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

2(R)-{2-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy}-3-phenyl propionyl-methionine methyl ester;

2(R)-{2-[1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl]pyrrolidin-3(S)-ethyl-2(S)-ylmethoxy}-3-phenyl propionyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine methyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine;

N-[1-(seryl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(D-alanyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-carbonyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(isoasparagyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(3-pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2-pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester ;

N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(seryl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(D-alanyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-imidazol-4-carbonyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine ;

N-[1-(isoasparagyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-pyridylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylmethyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-aminoethyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(2-thienyl)alanine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(trifluoromethyl)alanine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(2(S)-amino-4-acetylamino)butyric acid ;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N,N-dimethyl)glutamine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-methoxybenzyl)glycyl-methionine;

N-[1-(glycyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine;

N-((4-imidazolyl)methyl-(2S)-pyrrolidinylmethyl)-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(2-thienyl)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N,N-dimethyl)glutamine methyl ester ;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(trifluoromethyl)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(2(S)-amino-4-acetylamino)butyric acid methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]- N-(benzyl)glycyl-methionine methyl ester;

N-[1-(glycyl) pyrrolidin-3(S)-ethyl-2(S)-ylmethyl]-N-(benzyl)glycyl-methionine methyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine cyclohexyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine benzyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine ethyl ester;

N-[1-(sarcosyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(N,N-dimethylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine (2-pyridylmethyl) ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine (1-glyceryl) ester;

N-[1-L-prolylpyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(L-prolyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1-morpholinoacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(1-morpholinoacetyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(3-piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(3-piperidinecarbonyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(2-pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(2-pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-pyridylglycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(4-pyridyl(N-methyl)glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine methyl ester;

N-[1-(4-pyridyl(N-methyl)glycyl)pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylpropionyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine;

N-[1-(1H-imidazol-4-ylpropionyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine methyl ester;

N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine;

N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine methyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-acetylamino)alanine cyclohexyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N-methyl)glutamine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylmethyl)glycyl-(N-methyl)glutamine methyl ester ;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-methylcarbonylamino)alanine;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-methylcarbonylamino)alanine methyl ester ;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-methylsulfonylamino)alanine;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-methylsulfonylamino)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-propionylamino)alanine ;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-propionylamino)alanine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-pyrrolidinon-1-ylamino)alanine;

N-[1-(1H-imidazol-4-ylacetyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-(β-pyrrolidinon-1-ylamino)alanine methyl ester ;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(3-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methoxybenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-cyanobenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(3-cyanobenzyl)glycyl-methionine methyl ester ;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(4-cyanobenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

N-[1-(glycyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(2-cyanobenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methylbenzyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-methylbenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-trifluoromethylbenzyl)glycyl-methioninc;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(2-trifluoromethylbenzyl)glycyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylsulfonyl)glycyl-methionine;

N-[1-(1H-imidazol-4-ylacetyl)pyrrolidin-2(S)-ylmethyl]- N-(1-naphthylsulfonyl)glycyl-methionine methyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 4-N-methylpiperidinyl ester;

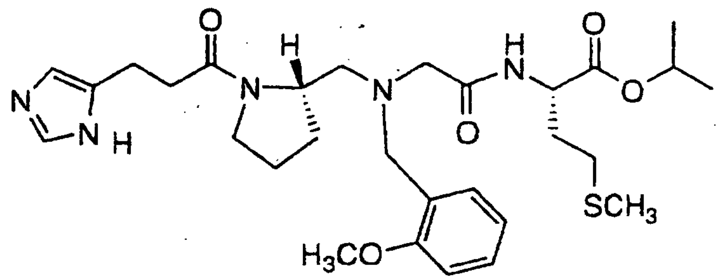
N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine tert-butyl ester;

N-[1-(glycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine 3-pentyl ester;

N-[1-(4-pyridylglycyl) pyrrolidin-2(S)-ylmethyl]-N-(1-naphthylmethyl)glycyl-methionine isopropyl ester;

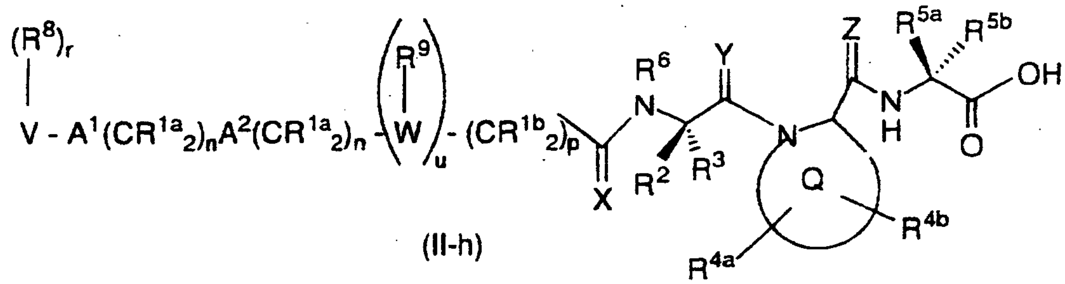
N-[1-(1H-imidazol-4-ylpropionyl)pyrrolidin-2(S)-ylmethyl]- N-(1l-naphthylmethyl)glycyl-methionine isopropyl ester;

N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester

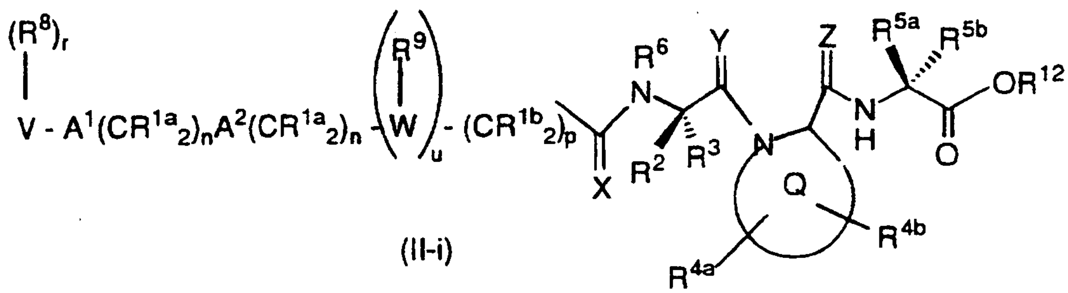


or a pharmaceutically acceptable salt thereof.

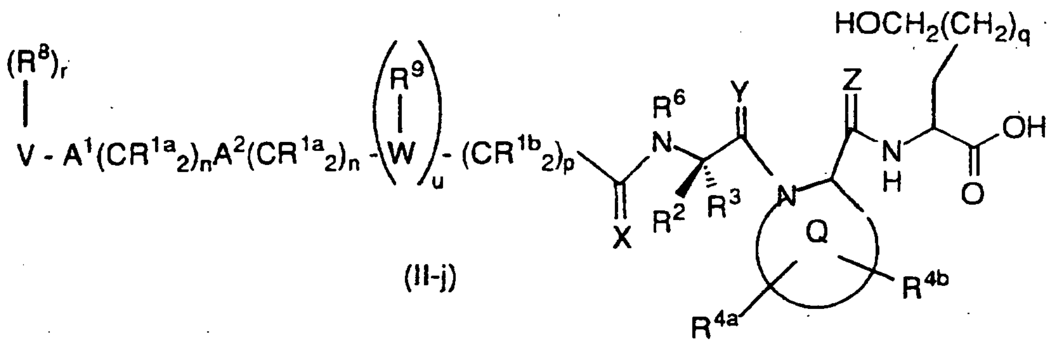
11. A method of treating cancer in accordance with claim 6 wherein the farnesyl transferase inhibiting compound is
(c) a compound represented by one of formulas (II-h) through (II-k):



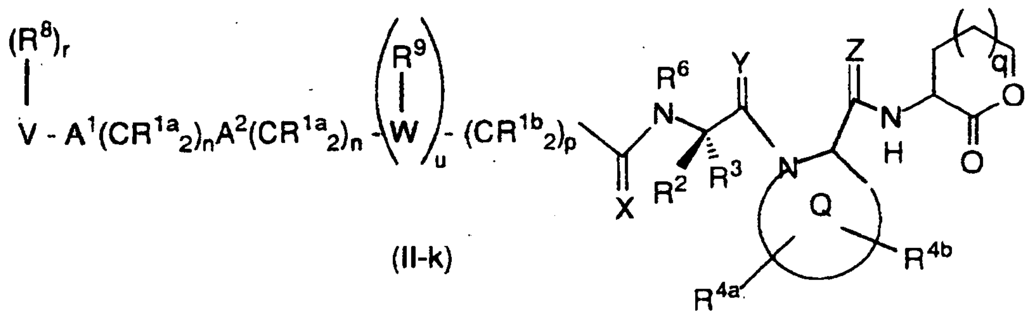
(II-h)



(II-i)



(II-j)



(II-k)

selected from the group consisting of:
N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester;

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine;

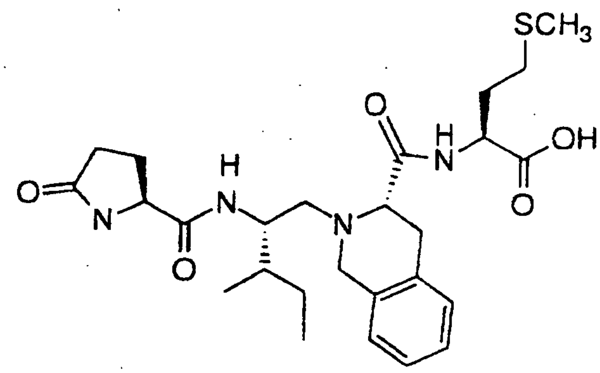
N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine methyl ester;

N-[1-(1H-imidazol-4-ylacetyl)-3(S)-ethylpyrrolidin-2(S)-ylmethyl]-prolyl-methionine;

N-[1-glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine methyl ester;

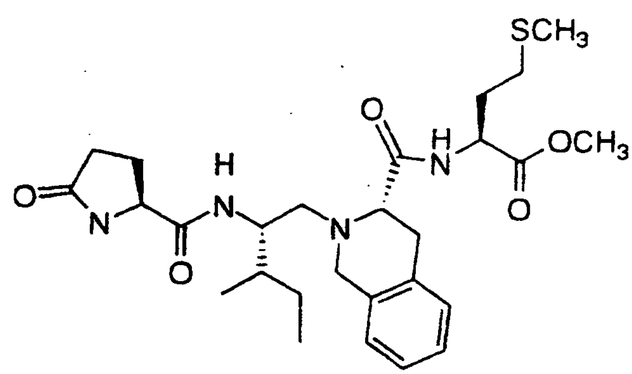
N-[1-glycylpyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine;

N-[L-pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine



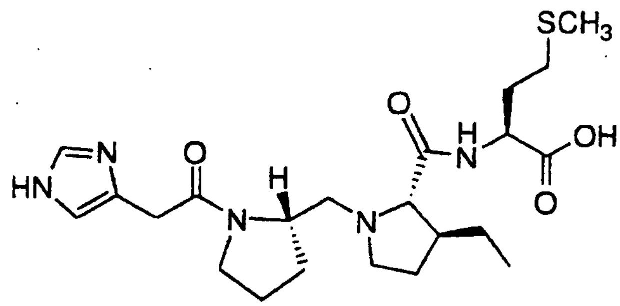
;

N-[L-pyroglutamyl-2(S)-amino-3(S)-methylpentyl]-1,2,3,4-tetrahydro-3(S)-isoquinolinecarbonyl-methionine methyl ester



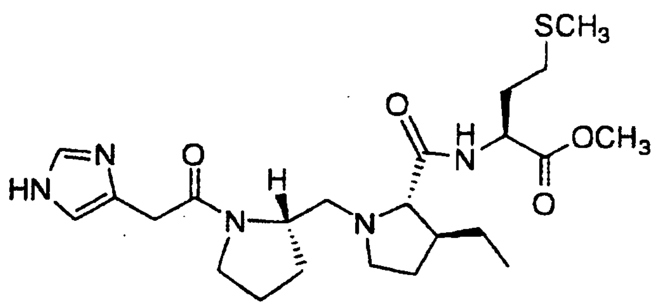
;

N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S)-ylmethyl]-3(S)-ethylprolyl-methionine



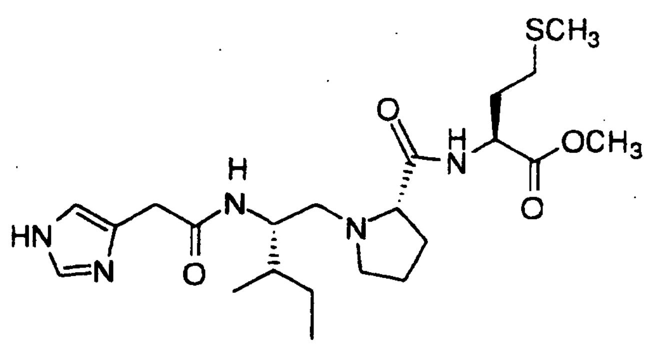
;

N-[1-(1H-imidazol-4-ylacetyl)-pyrrolidin-2(S-)ylmethyl]-3(S)-ethylprolyl-methionine methyl ester



;

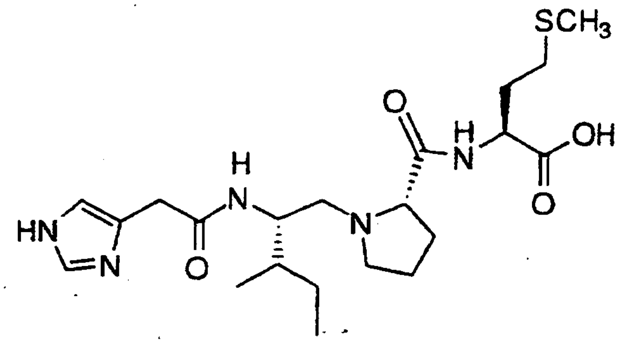
N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine methyl ester



;

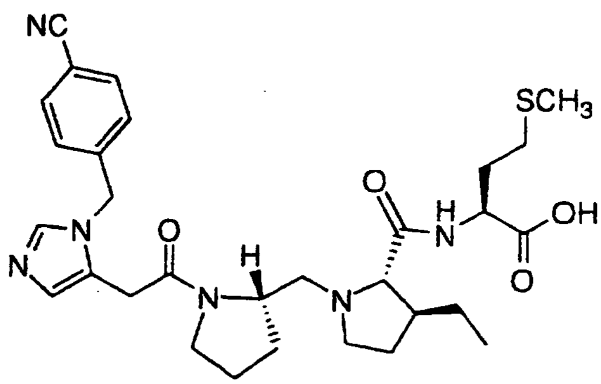
and

N-[(1H-imidazol-4-ylacetyl-2(S)-amino)-3(S)-methylpentyl]-prolyl-methionine



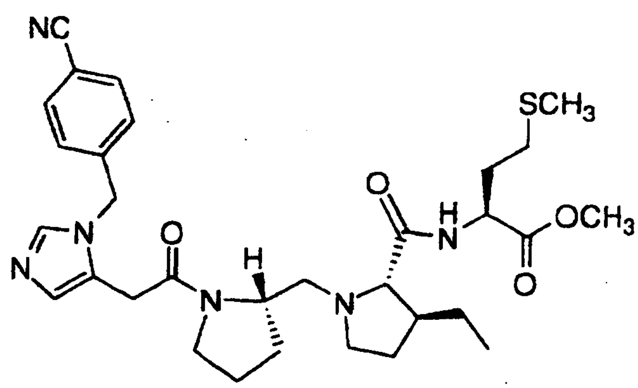
;

(N-[1-cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine;



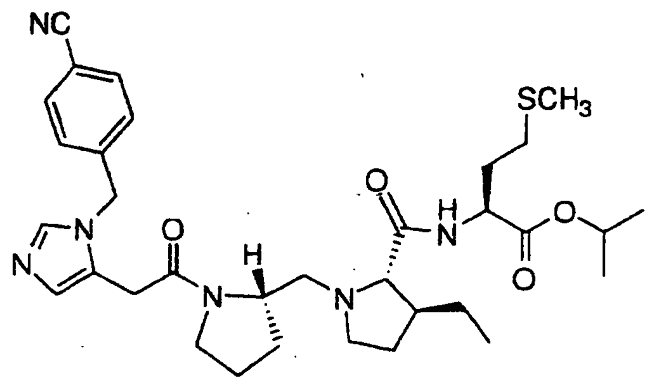
;

(N-[1-cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine methyl ester;



;

(N-[1-cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester, and



;

or a pharmaceutically acceptable salt thereof.

12. A method in accordance with claim 1 wherein the farnesyl protein transferase inhibiting compound is selected from the group consisting of:

(S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-imidazolylmethyl]-5-[2-(methanesulfonyl)ethyl]-2-piperazinone dihydrochloride;

1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)imidazolyl-methyl]-2-piperazinone dihydrochloride;

N-[1-(1H-Imidazol-4-propionyl) pyrrolidin-2(S)-ylmethyl]-N-(2-methoxybenzyl)glycyl-methionine isopropyl ester;

(N-[1-Cyanobenzyl)-1H-imidazol-5-yl)acetyl]pyrrolidin-2(S)-ylmethyl]-3(S)-ethyl-prolyl methionine isopropyl ester;

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-4-(2,3-dimethylphenyl)piperazin-5-one;

N-[2(S)-N'-(1-(4-Cyanophenyl-methyl)-1H-imidazol-5-ylacetyl)amino-3(S)-methylpentyl]-N-1-naphthylmethyl-glycyl-methionine methyl ester

and

2(S)-[2(S)-[2(R)-Amino-3-mercapto]propylamino-3(S)-methyl]-pentyloxy-3-phenylpropionyl-methionine sulfone isopropyl ester, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprised of a compound which inhibits MEK and a compound which inhibits farnesyl protein transferase.

14. A pharmaceutical composition which is comprised of a compound which inhibits MEK and farnesyl protein transferase.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08992

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/212, 218, 255, 307, 315, 343, 397, 422, 423; 540/492, 575, 609; 544/384, 385, 386; 546/139, 184, 276.4; 548/335.1, 576

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

APS SEARCH 1975- TO DATE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS COMPUTER SEARCH 1966- TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,352,705 A (DEANNA, deceased et al.) 04 October 1994, see entire document.	1-9, 11-14 --- 1-9, 11-14
X --- Y	US 5,439,918 A (deSOLMS et al.) 08 August, 1995, see entire document.	1-9, 11-14 --- 1-9, 11-14
X --- Y	US 5,491,164 A (deSOLMS et al.) 13 February 1996, see entire document.	1-9, 11-14 --- 1-9. 11-14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 JULY 1997	29 SEP 1997

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	IW for ZINNA N. DAVIS
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08992

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P ------ Y, P	US 5,525,625 A (BRIDGES et al.) 11 June 1996, see entire document.	1-9, 11-14 -------------- 1-9, 11-14
X --- Y	ALESSI et al. PD098059 Is a Specific Inhibitor of the Activation of Mitogen-activated Protein Kinase Kinase in Vitro and in Vivo. The Journal of Biological Chemistry. 17 November 1995. Volume 270, Number 46, pages 27489-27494, see entire document.	1-9, 11-14 -------------- 1-9, 11-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08992

Box I Observations where certain claims were found unsearchable (Continuation of item 1 f first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 10 is missing.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08992

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 211/06, 213/02, 223/02, 233/06, 241/02, 243/06, 401/02, 403/02; A61K 31/33, 31/40, 31/415, 31/44, 31/445, 31/47, 31/495

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/212, 218, 255, 307, 315, 343, 397, 422, 423; 540/492, 575, 609; 544/384, 385, 386; 546/139, 184, 276.4; 548/335.1, 576